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Review Article

A Systematic Review and Meta-analysis of Non-pharmacological Methods to Manipulate Experimentally Induced Secondary Hypersensitivity[1]

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Abstract: **This systematic review and meta-analysis investigated the effects of non-pharmacological manipulations on experimentally induced secondary hypersensitivity in pain-free humans. We investigated the magnitude (change/difference in follow-up ratings from pre-manipulation ratings) of secondary hypersensitivity (primary outcome), and surface area of secondary hypersensitivity (secondary outcome), in 27 studies representing 847 participants. Risk of bias assessment concluded most studies (23 of 27) had an unclear or high risk of performance and detection bias. Further, 2 (of 27) studies had a high risk of measurement bias. Datasets were pooled by the method of manipulation and outcome. The magnitude of secondary hypersensitivity was decreased by diverting attention, anodal transcranial direct current stimulation, or emotional disclosure; increased by directing attention toward the induction site, nicotine deprivation, or negative suggestion; and unaffected by cathodal transcranial direct current stimulation or thermal change. Area of secondary hypersensitivity was decreased by anodal transcranial direct current stimulation, emotional disclosure, cognitive behavioral therapy, hyperbaric oxygen therapy, placebo analgesia, or spinal manipulation; increased by directing attention to the induction site, nicotine deprivation, or sleep disruption (in males only); and unaffected by cathodal transcranial direct current stimulation, thermal change, acupuncture, or electroacupuncture. Meta-analytical pooling was only appropriate for studies that used transcranial direct current stimulation or hyperbaric oxygen therapy, given the high clinical heterogeneity among the studies and unavailability of data. The evidence base for this question remains small. We discuss opportunities to improve methodological rigor including manipulation checks, structured blinding strategies, control conditions or time points, and public sharing of raw data.**

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Perspective: ***We described the effects of several non-pharmacological manipulations on experimentally induced secondary hypersensitivity in humans. By shedding light on the potential for non-pharmacological therapies to influence secondary hypersensitivity, it provides a foundation for the development and testing of targeted therapies for secondary hypersensitivity.***

Key words: *Secondary hyperalgesia, Hypersensitivity, Central senitization, Pain, Pinprick pain, Complementary therapies*

Persistent pain is common and contributes to disability. The Global Burden of Diseases 2016 study reported low back pain and migraine to be 2 of the 5 leading causes of years lived with disability.[1] Moreover, persistent pain is associated with reduced quality of life,[2,3] and depression, and anxiety.[3,4]

Pharmacotherapy is the mainstay intervention for the management of persistent pain; however, the response to recommended pharmacotherapies is poor.[5,6] In fact, between 2005 and 2010, there was a 66% increase in published trials investigating pharmacological treatments for neuropathic pain [5] yet, despite this increase in research, there has not been an improvement in the management of neuropathic pain with pharmacotherapy.[5]

There are alternative options to pharmacotherapy for managing different persistent pain conditions. For example, treatments such as cognitive behavioral therapy,[7] physical exercise,[8] and invasive and non-invasive cortical stimulation have all been found to decrease the intensity of persistent neuropathic pain. However, research into non-pharmacological treatments is often of poor quality and generates conflicting data.[9-11]

Irrespective of the treatment modality, the key to effective management of persistent pain may be better targeting of treatment to the specific pathophysiological mechanisms underlying particular features of persistent pain.[12] Human surrogate models of secondary hyperalgesia, a prominent clinical feature of neuropathic, nociplastic, and inflammatory pain, offer an opportunity to undertake focused studies of a pain mechanism in healthy individuals rather than in the complex phenotypes that are present in the clinical setting.[13] Clinically, secondary hyperalgesia is common in patients with persistent pain, particularly in patients with fibromyalgia,[14] temporomandibular joint disorder,[15] and complex regional pain syndrome.[16] Assessment of secondary hyperalgesia by clinicians serves as an indicator of spinal cord upregulation.[17,18] Indeed, various methods can safely induce short-lived experimental secondary hyperalgesia in humans, including high-frequency electrical stimulation,[19,20] low-frequency electrical stimulation,[21] application of topical capsaicin,[22] intradermal capsaicin injection,[23] and superficial burn injury.[24] Pharmacological and non-pharmacological interventions can then be used to manipulate the experimental secondary hyperalgesia before, during, or after the induction. This experimental approach can shed light on factors that influence secondary hyperalgesia and inform the understanding of mechanisms underlying secondary hyperalgesia.

Experimental pain studies investigating this line of inquiry frequently use 2 similar but different terms: secondary hyperalgesia and secondary hypersensitivity. Secondary hyperalgesia refers to an increased perception of stimuli that were perceived as *painful* before an induction, in the area surrounding the induction. However, in experimental studies, stimulation to pinprick probes and von Frey filaments are inconsistently perceived as being painful before inductions. As such, the term *hypersensitivity,* rather than hyperalgesia, more accurately describes the increased perception of stimulation to pinprick probes and von Frey filaments after induction. Therefore, we opted to divert from the terminology used in our protocol and instead use *secondary hypersensitivity* throughout this paper.

The aim of this systematic review and meta-analysis was to identify, collate, and describe all the published studies that have applied non-pharmacological manipulations intended to influence experimentally induced secondary hypersensitivity in human participants without clinical pain. This thorough examination of the literature is anticipated to yield a resource that summarizes the current body of evidence, provides pooled effect size estimates where possible, identifies gaps in knowledge and opportunities for further inquiry.

Methods

This systematic review and meta-analysis were planned and conducted according to the guidelines of the Cochrane Collaboration.[25] The protocol was published in *Systematic Reviews* (https://doi.org/10.1186/s13643-019-1120-7) [26] before commencing the online search and was registered with PROSPERO (CRD42020146486) after conducting the online search and screening of articles but before conducting the risk of bias assessment and data extraction. We followed the reporting guidelines for preferred reporting items for systematic reviews and meta-analyses[27] (Supplementary File 1).

The protocol described a review of studies that used either non-pharmacological or pharmacological manipulations of secondary hypersensitivity. Given the number of eligible studies, we focus here on the studies that tested non-pharmacological manipulations only. The remaining studies will be reviewed in a separate publication (in preparation). To classify the manipulations, we acknowledged that both pharmacological and non-pharmacological manipulations influence normal physiological functioning, and so used the mode of

administration to classify the manipulations. For pharmacological manipulations, participants had to have received a chemical substance via ingestion, injection, or topical administration. For example, ingestion of a liquid containing a high concentration of lipids would be classified as a *pharmacological* manipulation. Conversely, nicotine deprivation in smokers would be considered a *non-pharmacological* manipulation because, although nicotine deprivation would influence normal physiological functioning, it does not involve ingestion, injection, or topical administration of a chemical substance.

Types of Studies

Prospective experimental studies were eligible—that is, studies that attempted to experimentally induce and manipulate secondary hypersensitivity for the purpose of studying the effects of the manipulation on experimentally induced secondary hypersensitivity. The manipulation had to be performed in the context of an experiment, such that the secondary hypersensitivity was not a naturally occurring clinical phenomenon. That is, participants must have begun the study without any secondary hypersensitivity present. Studies must have assessed secondary hypersensitivity within 120 minutes after induction (so as to avoid missing the expected peak of secondary hypersensitivity after experimental induction). Published, in-press, or accepted records for which title, abstract, and full-text versions were available in English were eligible for inclusion.

Types of Study Participants

Data from human participants without clinical pain conditions were included. No restrictions were placed on the ages of participants, but data from adults were to be treated separately from data from children (< 18 years old). Data from non-human studies were excluded.

Types of Interventions

Data were included from experimental studies that aimed to manipulate secondary hypersensitivity. Studies that manipulated secondary hypersensitivity as 1 step in a larger study were considered eligible only if suitable baseline/control data were available to estimate the effect of the manipulation on ratings to mechanical punctate stimulation.

Types of Outcome Measures

Primary Outcome

The protocol stated that the primary outcome was mechanical secondary hypersensitivity—specifically, ratings to mechanical punctate stimulation in the area surrounding the induction site. We were interested in the magnitude of secondary hypersensitivity as captured by a change in mechanical punctate stimulation from pre-manipulation levels. Studies need to have provided a control for the manipulation. For example, ratings of mechanical punctate stimulation before and after manipulation (within-subject comparison) or ratings of mechanical punctate stimulation after one group received the manipulation and the other a sham (between-group comparison). Ideally, studies should also have included a control condition or time point for the induction so as to capture the effect of the induction prior to manipulation. However, an unfortunate limitation of the literature base is that controls for the induction are rarely included, so we accepted data from studies as long as an accepted induction known to induce secondary hypersensitivity was clearly used and the timing of manipulation relative to induction was sufficient to make it likely that a change in rating attributable to the manipulation would likely reflect a change in the induced secondary hypersensitivity.

Secondary Outcomes

We also gathered data on 4 other outcomes. These were: 1) surface area of secondary hypersensitivity, as measured using reproducible methods (such as a radial lines approach[22,28,29]); 2) time course of secondary hypersensitivity; 3) pain elicited from the manipulation (eg, pain from a thermal manipulation); and 4) adverse events (eg, skin damage, other adverse reaction(s)) associated with the manipulation. The time course of secondary hypersensitivity is clinically relevant in that it gives insight into the duration of secondary hypersensitivity. It is clinically important to know if an intervention reduces the duration of the magnitude and/or surface area of secondary hypersensitivity.

Pain was defined as "an unpleasant sensory and emotional experience associated with actual or potential tissue damage, or described in terms of such damage".[30] Pain must have been assessed by participants' self-report.

Screening

Electronic Searches. The following electronic databases were searched (on June 24, 2019, updated October 01, 2019, August 27, 2020, and September 29, 2022) with a strategy that spanned the time from their inception to the date of the search: Biosis (via Web of Science), PubMed (includes MEDLINE), Scopus, PsychArticles, PsychInfo, Cochrane library, Web of Science Core (use to search and then use menu on left to filter for Core option and Biosis). The search strategy was: (["human*" OR "women" or "woman" OR "man" OR "men" OR "participant*" OR "volunteer* OR individual*"] OR "normal skin" OR "healthy skin") AND ("secondary hyperalgesia" OR "punctate hyperalgesia" OR "pinprick pain" OR "pinprick hyperalgesia" OR "mechanical hyperalgesia" OR "mechanical pain" OR "heat hyperalgesia" OR "neurogenic hyperalgesia"). All terms were searched for in the title, keywords, or abstract.

Other Sources. Reference lists of eligible studies were screened to check for other eligible studies that may have been missed by the electronic searches. Experts in the field, and the corresponding authors of the most recent narrative reviews on experimental induction and manipulation of secondary hypersensitivity, were

contacted to ask for their assistance in identifying any missed studies. In anticipation of a paucity of literature, the protocol had planned to request unpublished data from laboratories that have published extensively on these techniques. Given the abundance of published studies available, this step was not followed (protocol deviation 1 of 4). However, we did request data directly from authors where published records did not provide enough precision.

Data Collection and Analysis

Data Management. Originally, the protocol specified the use of the online systematic review facility (http://syrf.org.uk/) to manage the review process. However, given this platform is generally *not* used for human studies, it proved difficult for use in this review, so we switched to the Covidence (https://covidence.org/) online software to manage the review process (protocol deviation 2 of 4).

Study Selection. Identified records were independently screened for eligibility by 2 of 3 reviewers (GJB, PCC, and LM) in 2 sequential stages: screening of title and abstracts (Stage 1) and screening of full texts (Stage 2). A customized eligibility form (Supplementary File 2) was used in Stage 2. Any disagreements about study inclusion were resolved by discussion or by adjudication from a fourth reviewer (VJM).

Risk of Bias Analysis. Risk of bias assessments were independently conducted by 2 of 3 reviewers (GJB, FS, and LM) to assess the quality of the methods and identify potential flaws in the study design or reporting that might render the results unreliable for the purposes of answering the question of the current review.[31] The reviewers piloted the risk of bias assessment form on 3 studies and adapted it prior to formal application to all included studies. The assessment considered the risks of selection, sampling determination bias (added after protocol had been published; protocol deviation 3 of 4), performance, detection, attrition, measurement, and reporting bias, and other sources of bias. The criteria used to estimate the risk of bias were based on the recommendations from the Cochrane Collaboration,[32] known quality instruments (eg, the CONSORT[33] and STROBE[34] statements as relevant), and on known areas of bias relevant to the study design used,[35] and were specified in the risk of the bias assessment tool and guide (Supplementary File 3). The appraisals of the 3 reviewers were compared and any disagreements resolved through discussion or by adjudication from a fourth reviewer (VJM).

Data Extraction. Data were extracted independently and in duplicate from each included study, using a standardized form (Supplementary File 4) by 2 of 3 reviewers (GJB, FS, and LM). This standardized data extraction form had been piloted and refined using 3 studies before formal data extraction. Study authors were contacted to obtain data that were unavailable or unclear from the published texts. If no reply was received within 6 weeks, or relevant data were not provided within 6 weeks of the first reply, the data were considered unavailable. Any published data that seemed implausible were verified directly with the corresponding author where possible.

Data Analysis. Data were analyzed to 1) determine the effect of each manipulation method, 2) pool and compare data where possible and sensible, 3) facilitate relative ranking of manipulations to compare the potency of the various manipulation procedures for influencing secondary hypersensitivity, and 4) detect publication bias. Data on the magnitude of secondary hypersensitivity were handled separately from those on the area of secondary hypersensitivity. The protocol specified that, if the quantity and quality of data allowed, the pooled effect size estimates would be compared to rank the different manipulations in order of potency and risk. We planned to use funnel plots to examine for publication bias.

Rescaling of Rating Scales. A wide variety of rating scales are used to assess the severity of pain. To allow for descriptive comparison across ratings data, all ratings from 0 to 100 rating scales were rescaled to 0 to 10, by dividing by 10. Rating data from studies that used alternative scales—such as the −50 to +50 Sensation and Pain Rating Scale—were managed separately.

Pooling of Data and Measures of Manipulation Effects. The protocol had anticipated the subgrouping of studies into manipulations with localized effects, systemic effects, and time-limited effects to determine the potency of the manipulation methods. However, given the records retrieved and to maximize clarity, we opted to subgroup by the hypothesized direction of manipulation effect (ie, to increase or decrease) on 1) magnitude and 2) area of secondary hypersensitivity (protocol deviation 4 of 4). We felt that this approach would provide the most comprehensive description of the effects of the manipulation on magnitude and area of secondary hypersensitivity than the previously planned subgroups, given that the purpose of this review was to clarify the effects of factors that may influence the mechanisms of secondary hypersensitivity. Therefore, we have grouped studies according to whether the hypothesized effect of the manipulation was to decrease or increase the magnitude and/or area of secondary hypersensitivity, and then by the manipulation procedure. Across the eligible studies, the magnitude and surface area of secondary hypersensitivity had been assessed at different times after the induction. It was not possible to determine the time point of the peak effect of each manipulation, but it was possible to determine the time point of the peak effect of each induction by using the control data. Therefore, we extracted data for the time point at which the control group/condition showed the

highest ratings to mechanical punctate stimulation or the greatest surface area of secondary hypersensitivity. We used the mean ± SD and sample sizes to calculate the standardized mean difference (because it is recommended for continuous data where different scales have been used[25]). We used a random effects model to allow for anticipated heterogeneity between studies. When studies did not provide mean ± SD ratings to mechanical punctate stimulation or surface area of secondary hypersensitivity, we converted alternative measures of central tendency and spread as per the guidelines in the Cochrane Handbook. We used the RevMan software,[36] version 5.3, to convert data to mean ± SD (where applicable), pool data, and generate forest plots using a random effects model.

Assessment of the Quality of the Body of Evidence. The quality of the body of evidence for each manipulation was assessed using the GRADE criteria[37] and the GRADEpro GDT software (www.gradepro.org). In keeping with the GRADE guidelines, the quality of the body of evidence was estimated for each outcome, where more than one study was available for a certain manipulation. The assessment was determined based on 1) risk of bias, 2) directness, 3) consistency of results across studies, and 4) reporting precision. For each factor, studies are categorized as having *'no', 'serious' or 'very serious'* limitations. Factors graded as having *'serious'* limitations result in a downgrade of 1 level for the body of evidence. Last, the grade for the certainty of the body of evidence will be determined as high—"further research is very unlikely to change our confidence in the estimate of effect", moderate—further research is likely to have an important impact on our confidence in the estimate of the effect and may change the estimate, low—"further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the estimate", or very low—"any estimate of effect is very uncertain".

Results

Results of Search

An initial literature search (conducted on June 24, 2019) yielded a total of 4,809 records, of which 2,251 remained after duplicates were removed. An additional 666 studies were identified when the search was updated (September 29, 2022) and one study was identified through direct communication with experts in the field. Therefore, a total of 2,918 records investigating non-pharmacological *and* pharmacological manipulations were included in the title/abstract screening. Thereafter, 268 articles went to the full-text screening. Of these, 169 records were eligible for inclusion. Of the 169 records eligible for inclusion, 24 reported on non-pharmacological manipulations, and therefore, are reported here, the remaining 145 records reported on pharmacological manipulations.

Two (of 24) records yielded more than one eligible dataset: Torta et al[21] reported on 3 studies, of which studies 2 and 3, 2 were eligible for inclusion while study 1 was not eligible for inclusion in this review, and Yucel et al[38] reported on 3 studies, of which all were eligible for inclusion in this review. Therefore, the total number of studies included in this review was 27. A preferred reporting item for systematic reviews and meta-analyses flow diagram (Fig 1) outlines the inclusion process.

Included Studies

Types of Studies

Table 1 summarizes the characteristics of the eligible studies. Of the 27 eligible studies, the study designs included crossover (n = 12), Experiments 1, 2, 3,[24,38–46] between-group (n = 8),[47–54] and within-subject (without crossover) comparisons (n = 7).[21,23,55–58]

Notably, based on our eligibility criteria, Bedwell, Louw et al, 2022 were eligible for inclusion in this review and the study's methodology and risk of bias assessment have been reported here. However, Bedwell, Louw et al, 2022 reported their threat manipulation to be ineffective; therefore, their data on the influence of their manipulation the change in pinprick perceptions in the secondary zone and surface area of secondary hypersensitivity were not useful for answering our research question and were not reported in this reviews' outcomes.

Participants

A total of 847 participants (460 males, 387 females) were represented in the 27 eligible studies. All participants were adults (> 18 years old). Age data could not be pooled because the reporting of descriptive statistics varied; participants' ages are shown by the study in Table 1. Five (of the 27) studies included male participants only. One study included female participants only, with further selection for participants with a history of trauma.[51] This biased sample was appropriate to the study's question but not to the aim of this review.

Types of Interventions

Across the 27 eligible studies, 6 different methods were used to induce secondary hypersensitivity: burn injury (n = 6), topical capsaicin (n = 5), high-frequency electrical stimulation (n = 5), heat with topical capsaicin (n = 4), intradermal capsaicin injection (n = 4), and low-frequency electrical stimulation (n = 3). A variety of manipulations was used to influence the magnitude and/or area of the experimentally induced secondary hypersensitivity: thermal stimulation (n = 6), diversion of participants' attention (n = 4), transcranial direct current stimulation (n = 4),

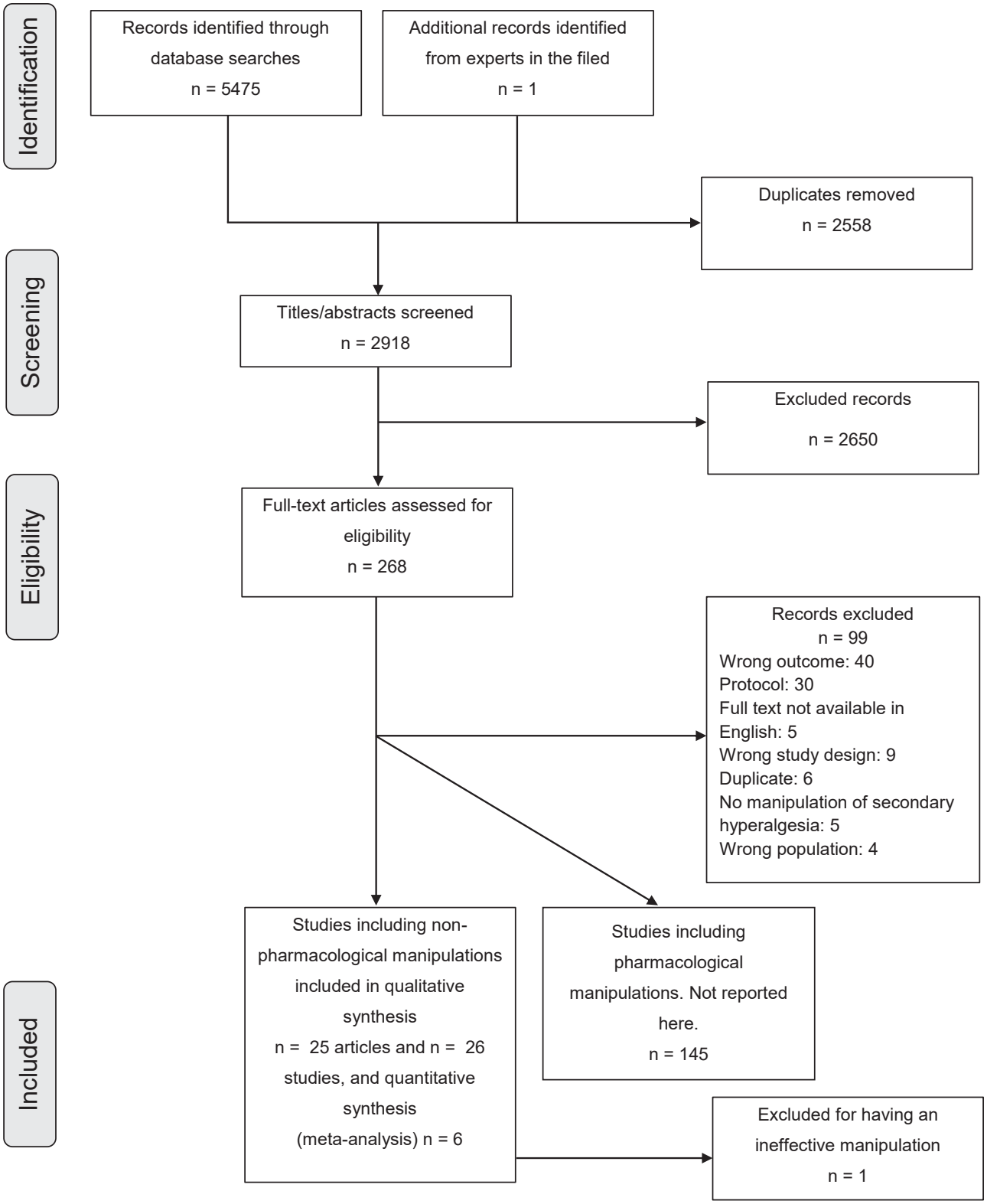

Figure 1. Preferred reporting items for systematic reviews and meta-analyses (PRISMA) flow diagram.

hyperbaric oxygen therapy (n = 2), acupuncture (n = 1), electroacupuncture (n = 1), cognitive behavioral therapy (n = 1), directing participants' attention towards the induction site (n = 1), placebo analgesia (n = 1), spinal manipulation therapy (n = 1), written emotional disclosure (n = 1), negative suggestion (n = 1), manipulation of threat (n = 1), nicotine deprivation (n = 1), and sleep disruption (n = 1). Table 2 provides a summary of each study's induction and manipulation methods.

Table 1. Summary of Studies' Characteristics

Study	Study design	Sample size determination (Total: male; female)	Age of participants mean ± SD, (95% CI), or (range) unless marked as median	Secondary hypersensitivity induction method	Secondary hypersensitivity manipulation method	Magnitude of SH outcome measurement method	Rating scale	Area of SH outcome measurement method
Manipulation: thermal stimulation (n = 6)								
Baron et al (1999)	Within-subject—comparison of whole body heating with whole body cooling.	Not reported (10: 10;0)	Not reported	Intradermal capsaicin injection	Whole-body heating and cooling with a thermal suit.	250 mN von Frey filament.	0 to 10	4 radial lines. Sensitivity was assessed using 250 mN von Frey filament.
Pud et al (2006)	Within-subject—comparison of outcomes a) after induction but before cooling and b) after induction and after cooling.	Not reported (14: 9;5)	24.5 (20–35)	Intradermal capsaicin injection	Cooling of the induction site after induction.			6 radial lines at 60° angles. Sensitivity was assessed using 60.0 g von Frey filament.
Werner et al (2002)	Within-subject—burn injury induced at bilateral calves but cooling performed at one calf only. Comparison of outcomes assessed at the a) site with cooling and at the b) site with no cooling.	Based on power calculations. (24: 24;0)	Not reported	Burn injury	Cooling of the induction site after induction.	535 mN von Frey filament.	0 to 100	4 radial lines. Sensitivity was assessed using 535 mN von Frey filament.
Yucel et al (2001) Experiment 1	Crossover—comparison of outcomes with a) thermal stimulation before and after induction and b) thermal stimulation before induction only.	Not reported (10: 7;3)	25 ± 5.7 (21–30)	Topical capsaicin	Heating of the induction site before and twice after induction.			Sensitivity was assessed using 75.9 g von Frey filament. Specific methods of assessing area were not reported.
Yucel et al (2001) Experiment 2	Crossover—comparison of outcomes with a) thermal stimulation before and after induction and b) thermal stimulation before induction only.	Not reported (10: 8;2)	25 ± 4.2 (21–34)	Intradermal capsaicin injection	Heating of the induction site before and twice after induction.			Sensitivity was assessed using 75.9 g von Frey filament. Specific methods of assessing area were not reported.
Yucel et al (2001) Experiment 3	Crossover—comparison of outcomes with a) thermal stimulation before and after induction and b) thermal stimulation before induction only.	Not reported (10: 7;3)	25 ± 3.7 (21–34)	Burn injury	Heating of the induction site before and twice after induction.			Sensitivity was assessed using 75.9 g von Frey filament. Specific methods of assessing area were not reported.
Manipulation: diversion of attention (n = 4)								
Kobor et al (2009)	Crossover—comparison of outcomes assessed a) during diversion of attention with ratings assessed b) during no diversion of attention.	Not reported (16: 11;5)	22.9 (19–25)	Heat and topical capsaicin	Diversion of attention after induction and during the assessment.	180 g and 300 g von Frey filament.	0 to 10	

Table 1 (*Continued*)

Study	*Study design*	*Sample size determination (Total: male; female)*	*Age of participants mean ± SD, (95% CI), or (range) unless marked as median*	*Secondary hypersensitivity induction method*	*Secondary hypersensitivity manipulation method*	*Magnitude of SH outcome measurement method*	*Rating scale*	*Area of SH outcome measurement method*
Torta et al (2020, Experiment 2)	Within-subject—comparison of outcomes assessed a) before the induction and the Eriksen Flanker test and b) after the induction and the Eriksen Flanker test	Based on comparable studies (19: 4;15)	Median 22 (18–40)	Low-frequency electrical stimulation	Diversion of attention using Eriksen Flanker test during the induction.	128 mN pinprick stimulator.	0 to 100 rating scale with '50' representing the transition between non-painful (< 50) and painful (> 50).	
Torta et al (2020, Experiment 3)	Within-subject—comparison of outcomes assessed a) before the induction and the N-back test and b) after the induction and the N-back test.	Based on comparable studies (21: 11;10)	Median 26 (19–36)	Low-frequency electrical stimulation	Diversion of attention using modified version of an N-back task during the induction.	128 mN pinprick stimulator	0 to 100 rating scale with '50' representing the transition between non-painful (< 50) and painful (> 50).	
Mehesz et al 2021	Crossover—comparison of outcomes assessed a) during diversion of attention and ratings assessed, b) during no diversion of attention.	Not reported (19: 12;7)	26.7 ± 6.8	High-frequency electrical stimulation	Immersive 360° passive virtual reality arctic scene.	8, 16, 32, 64, 128, 256, and 512 mN pinprick stimulators	0 to 100	
Manipulation: transcranial direct current stimulation (n = 4)								
Hughes et al (2020)	Crossover—comparison of outcomes a) after induction and anodal and b) after induction and cathodal transcranial direct current stimulation.	Not reported (12: 5;7)	28.85 ± 2.14	Topical capsaicin	Anodal transcranial direct current stimulation over the primary motor cortex.	8, 16, 32, 64, 128, 256, and 512 mN pinprick stimulators	0 to 100	
Meeker et al (2019)	Crossover—comparison of outcomes a) after induction and anodal, b) after induction and cathodal, and c) after induction and sham transcranial direct current stimulation.	Based on power calculations (27: 16;11)	25 (20–35)	Heat and topical capsaicin	Anodal and cathodal transcranial direct current stimulation over the primary motor cortex.	128, 256, and 512 mN pinprick stimulators	0 to 100	8 radial lines at 45° angles. Sensitivity was assessed using 128 mN pinprick stimulator.
Steyaert et al 2022	Crossover—comparison of outcomes a) after induction and anodal, b) after induction and cathodal, and c) after induction and sham transcranial direct current stimulation.	Based on comparable studies (18: 7;11)	23.5 ± 4.0	High-frequency electrical stimulation	Anodal and cathodal transcranial direct current stimulation over the left dorsolateral prefrontal cortex.	128 mN pinprick stimulator	0 to 100	8 radial lines at 45° angles. Sensitivity was assessed using 128 mN pinprick stimulator.

Table 1 (*Continued*)

Study	Study design	Sample size determination (Total: male; female)	Age of participants mean ± SD, (95% CI), or (range) unless marked as median	Secondary hypersensitivity induction method	Secondary hypersensitivity manipulation method	Magnitude of SH outcome measurement method	Rating scale	Area of SH outcome measurement method
Vo et al (2021)	Crossover—comparison of outcomes a) after induction and anodal, and b) after induction and sham transcranial direct current stimulation.	Based on power calculations (39: 22;17)	26.87 ± 9.26	Low-frequency electrical stimulation	Anodal transcranial direct current stimulation over the 1) primary motor cortex, 2) dorsolateral prefrontal cortex, and 3) primary motor and dorsolateral prefrontal cortices concurrently.	40 g sharp tip with a calibrated spring mechanism	0 to 10	
Manipulation: hyperbaric oxygen therapy (n = 2)								
Rasmussen et al (2015)	Crossover—comparison of outcomes assessed a) after induction and after hyperbaric oxygen therapy and b) after induction and after control condition.	Based on power calculations (17: 17;0)	27.6 (25.1–30.2)	Burn injury	Hyperbaric oxygen therapy			8 radial lines at 45° angles. Sensitivity was assessed using 895 mN polyamide monofilament.
Wahl et al (2019)	Crossover—comparison of outcomes assessed a) after induction and after hyperbaric oxygen therapy and b) after induction and after control condition.	Based on power calculations (19: 19;0)	Median 26.1 (24.7–28.8)	Burn injury	Hyperbaric oxygen therapy			8 radial lines at 45° angles. Sensitivity was assessed using 512 mN pinprick stimulator.
Manipulation: acupuncture (n = 1)								
Rebhorn et al (2012)	Between-group—comparison of outcomes assessed a) after induction and acupuncture and b) after induction and control condition.	Not reported (50: 50;0)	24.8 ± 2.36 (20–30)	Intradermal capsaicin injection	Traditional Chinese Medicine acupuncture			Sensitivity was assessed using 256 mN von Frey filament. Specific methods of assessing area were not reported.
Manipulation: electroacupuncture (n = 1)								
Zheng et al (2019)	Between-group—comparison of outcomes assessed a) after induction and electroacupuncture and b) after induction and control condition.	Based on comparable studies (26: 15;11)	24 ± 3.9	Heat and topical capsaicin	Electroacupuncture			8 radial lines at 45° angles. Sensitivity was assessed a 4.93 g using von Frey filament.
Manipulation: cognitive behavioral therapy (n = 1)								
Salomons et al (2014)	Between-group—comparison of outcomes assessed a) after induction and after the 8th (final) cognitive behavioral therapy session and b) after induction and after control condition.	Not reported (34: 18;16)	(21–38)	Repetitive heat stimulation	Cognitive behavioral therapy			8 radial lines at 45° angles. Sensitivity was assessed using 256 mN von Frey filament.

Table 1 (*Continued*)

Study	Study design	Sample size determination (Total: male; female)	Age of participants mean ± SD, (95% CI), or (range) unless marked as median	Secondary hypersensitivity induction method	Secondary hypersensitivity manipulation method	Magnitude of SH outcome measurement method	Rating scale	Area of SH outcome measurement method
Manipulation: directing attention towards the induction (n = 1)								
Filbrich Broeke et al (2020)	Within-subject—comparison of outcomes assessed after induction a) at the experimental site and b) control site.	Based on comparable studies (25: 9;16)	23.1 ± 2.29 (18–29)	High-frequency electrical stimulation	Vibrotactile spatial attention task	128 mN pinprick stimulator	0 to 100 rating scale with '50' representing the transition between non-painful (< 50) and painful (> 50).	Measured along the proximal-distal and medial-lateral axis in mm. Sensitivity was assessed using 128 mN pinprick stimulator.
Manipulation: placebo analgesia (n = 1)								
Matre et al (2006)	Between-group and within-subject – comparison of outcomes assessed a) after induction and after placebo analgesia and b) after induction and after control condition; and comparison of outcomes c) after the induction but before the placebo analgesia and d) after the induction and after the placebo analgesia.	Not reported (29: 17;12)	(20–45)	Burn injury	Placebo analgesia			8 radial lines. Sensitivity was assessed using 84.4 g/mm^2 (pressure) von Frey filament.
Manipulation: spinal manipulation (n = 1)								
Mohammadian et al (2004)	Crossover—comparison of outcomes assessed a) after induction and after spinal manipulation and b) after induction and after control condition.	Not reported (20: 14;6)	27 (21–37)	Topical capsaicin	Spinal manipulation			6 radial lines at 60° angles. Sensitivity was assessed using 20.9 g von Frey filament.
Manipulation: written emotional disclosure (n = 1)								
You et al (2014)	Between-group—comparison of outcomes assessed a) after induction and after written emotional disclosure and b) after induction and after control condition.	Not reported (78: 0;78)	Mean ± SD With trauma history: 18.7 ± 0.6 Without trauma history: 18.8 ± 0.8	Topical capsaicin	Written emotional disclosure	2.9 N von Frey filament	0 to 10	8 radial lines at 45° angles. Sensitivity was assessed with 2.9 N von Frey filament.
Manipulation: negative suggestion (n = 1)								
van den Broeke et al (2014)	Between-group—comparison of outcomes assessed a) after induction and after negative suggestion and b) after induction and after control condition.	Not reported (30: 11;19)	23.5 (18–59)	High-frequency electrical stimulation	Negative suggestion	256 mN pinprick stimulator	0 to 10	

Table 1 (*Continued*)

Study	*Study design*	*Sample size determination (Total: male; female)*	*Age of participants mean ± SD, (95% CI), or (range) unless marked as median*	*Secondary hypersensitivity induction method*	*Secondary hypersensitivity manipulation method*	*Magnitude of SH outcome measurement method*	*Rating scale*	*Area of SH outcome measurement method*
Manipulation: threat manipulation (n = 1)								
Bedwell et al (2022)	Between-group—comparison of outcomes assessed a) after induction and after threat manipulation and b) after induction and after control condition.	Based on power calculations (26: 10;16)	21 (18–55)	High-frequency electrical stimulation	Manipulation of threat	128 and 256 mN pinprick stimulator	-50 to +50 rating scale with '0' representing the transition between non-painful (< 0) and painful (> 0).	8 radial lines at 45° angles. Sensitivity was assessed using 128 mN pinprick stimulator.
Manipulation: nicotine deprivation (n = 1)								
Ditre et al (2018)	Between-group—comparison of outcomes assessed a) after induction and nicotine deprivation and b) after induction and after control condition.	Not reported (165: 94;71)	41.12 ± 12.66	Topical capsaicin	Nicotine deprivation	300 g von Frey filament	0 to 10	8 radial lines at 45° angles. Sensitivity was assessed with 300 g von Frey filament.
Manipulation: sleep disruption (n = 1)								
Smith, Remeniuk et al (2018)	Crossover—comparison of outcomes assessed a) after induction and after sleep disruption and b) after induction and after control condition.	Not reported (79: 33;46)	27.18 ± 6.98	Heat and topical capsaicin	Sleep disruption			8 radial lines. Sensitivity was assessed using 5.18 (15.0 g) von Frey filament.

NOTE. Studies have been grouped by manipulation method.

Table 2. Summary of Induction and Manipulation Methods

Study	Induction of secondary hypersensitivity				Manipulation of secondary hypersensitivity					
					Experimental group			Control group		
	Method	Site	Duration	Dosage	Method	Duration	Dosage	Method	Duration	Dosage
Manipulation: thermal stimulation (n = 6)										
Baron et al (1999)	Intradermal capsaicin	Volar forearm		20 µL of a solution containing 0.5% capsaicin (100 µg)	Whole-body heating and cooling using a thermal suit	Not reported	Cooling: 12 °C, Heating: 50 °C			
Pud et al (2006)	Intradermal capsaicin	Volar forearm		50 µg/50 µL capsaicin	Cooling of the induction site after induction	30 s for each temperature	20, 10 and 0 °C			
Werner et al (2002)	Burn injury	Bilateral calf	7 min	47 °C	Cooling of the induction site after induction	30 min	8 °C	Non-active thermode	30 min	Ambient temperature
Yucel et al (2001, Experiment 1)	Topical capsaicin	Forearm	30 min	1.5 g of 1% capsaicin cream	Heating of the induction site before and twice after induction	Pre-conditioning: 5 min 1st post-conditioning: 2 min 2nd post-conditioning: 2 min	Pre-conditioning: 45 °C 1st post-conditioning: 39.2 SD 1.3 °C 2nd post-conditioning: 39.9 SD 2.8 °C	No pre- and post-conditioning heating		
Yucel et al (2001, Experiment 2)	Intradermal capsaicin	Forearm		50 µg in a volume of 0.2 ml	Heating of the induction site before and twice after induction	Pre-conditioning: 5 min 1st post-conditioning: 2 min 2nd post-conditioning: 2 min	Pre-conditioning: 45 °C 1st post-conditioning: 40.9 SD 2.3 °C 2nd post-conditioning: 41.8 SD 2.9 °C	No pre- and post-conditioning heating		
Yucel et al (2001, Experiment 3)	Burn injury	Forearm	7 min	47 °C	Heating of the induction site before and twice after induction	Pre-conditioning: 5 min 1st post-conditioning: 2 min 2nd post-conditioning: 2 min	Pre-conditioning: 45 °C 1st post-conditioning: 40.1 SD 2.8 °C 2nd post-conditioning: 41.9 SD 1.8 °C	No pre- and post-conditioning heating		
Manipulation: diversion of attention (n = 4)										
Kobor et al (2009)	Heat and topical capsaicin	Medial side lower leg	Heating of skin with a thermode at 45 °C for 5 min and then capsaicin cream for 45 min.	0.075% capsaicin cream	*High* and *low* attentional load face discrimination task performed during punctate mechanical stimulation.			Ignoring the face discrimination task during punctate mechanical stimulation.		

Table 2 (*Continued*)

Study	Induction of secondary hypersensitivity				Manipulation of secondary hypersensitivity					
					Experimental group			Control group		
	Method	Site	Duration	Dosage	Method	Duration	Dosage	Method	Duration	Dosage
Torta et al (2020, Experiment 2)	Low-frequency electrical stimulation	Volar forearm	2 min	2 Hz, pulse width 2 ms, intensity 15x detection threshold for single pulse	Modified version of an N-back task performed during induction	The task started 90 s before LFS and continued for approximately 90 s after LFS.				
Torta et al (2020, Experiment 3)	Low-frequency electrical stimulation	Volar forearm	2 min	2 Hz, pulse width 2 ms, intensity 15x detection threshold for single pulse	Eriksen Flanker Task performed during induction	The task started 90 s before LFS and continued for approximately 90 s after LFS.				
Mehesz, Karoui et al (2021)	High-frequency electrical stimulation	Volar forearm	5 x 1-second trains with 10-second intervals between trains	100 Hz, pulse width 2 ms, intensity 10x detection threshold for single pulse	Immersive 360° passive virtual reality arctic scene performed during punctate mechanical stimulation			Sham virtual reality consisting of the same arctic scene but displayed on a 2D monitor screen.		
Manipulation: transcranial direct current stimulation (n = 4)										
Hughes et al (2020)	Topical capsaicin	"left L5 dermatome, one-third the way along a line from the left lateral femoral epicondyle to the left lateral malleolus"	40 min	1% capsaicin cream	Transcranial direct current stimulation over the primary motor cortex	20 min	2 mA Current ramped up to 2 mA over a 10 s period, remained at 2 mA for the 20 min stimulation, and then 'faded-out'.	Sham transcranial direct current stimulation	20 min	Current ramped up to 2 mA over a 10 s period. After 30 s, the current faded out and turned off for the remainder of the 20-minute stimulation.
Meeker, Keaser et al (2019)	Topical capsaicin and heat	Lower foreleg	28 min	1 g of 10% capsaicin cream and simultaneous heating of skin with a thermode at 32 °C for 15 min and then for a further 23 min at a "target temperature", which was between participants' individual warmth detection threshold and heat pain thresholds.	Anodal and cathodal transcranial direct current stimulation over the motor cortex	20 min	1 mA Current ramped up to 2 mA over a 10 s period, remained at 2 mA for the 20 min stimulation, and then 'faded-out'.	Sham transcranial direct current stimulation	20 min	At the beginning of the 20-min stimulation, the current was ramped up to 1 mA for 30 s and then faded out. This was repeated at the end of the 20-min stimulation.

Table 2 (*Continued*)

Study	Induction of secondary hypersensitivity				Manipulation of secondary hypersensitivity					
					Experimental group			Control group		
	Method	Site	Duration	Dosage	Method	Duration	Dosage	Method	Duration	Dosage
Steyaert et al 2022	High-frequency electrical stimulation	Volar forearm	5 x 1-second trains with 10-second intervals between trains	100 Hz, pulse width 2 ms, intensity 20x detection threshold to a single pulse	Anodal and cathodal transcranial direct current stimulation over the left dorsolateral prefrontal cortex	20 min	2 mA Current ramped up to 2 mA over a 10 s period, remained at 2 mA for the 20 min stimulation, and then 'faded-out'.	Sham transcranial direct current stimulation	20 min	At the beginning of the 20-min stimulation, the current was ramped up to 2 mA for 30 s and then faded out. This was repeated at the end of the 20-minute stimulation.
Vo et al (2021)	Low-frequency electrical stimulation	Volar forearm	20 min	1 Hz, pulse width 0.5 ms, intensity set to a "evoke moderate (rating of 5/10 on VAS) pain"	Anodal transcranial direct current stimulation over the 1) primary motor cortex, 2) dorsolateral prefrontal cortex, and 3) primary motor and dorsolateral prefrontal cortices concurrently.	20 min	1 mA	Sham transcranial direct current stimulation	20 min	Current ramped up to 1 mA over a 30 second period. After 30 ss, the current faded out and turned off for the remainder of the 20-minute stimulation.
Manipulation: hyperbaric oxygen therapy (n = 2)										
Rasmussen et al (2015)	Burn injury	Calf	7 min	47 °C	Hyperbaric oxygen procedure	90 min with ± 5 min for compression and decompression	2.4 atmosphere, breathing 100% oxygen	Room air	90 min	1 atmosphere pressure, breathing 21% oxygen
Wahl et al (2019)	Burn injury	Calf	7 min	47 °C	Hyperbaric oxygen procedure	90 min with ± 5 min for compression and decompression	2.4 atmosphere, breathing 100% oxygen	Room air	90 min	1 atmosphere, breathing 21% oxygen
Manipulation: acupuncture (n = 1)										
Rebhorn et al (2012)	Intradermal capsaicin	Volar forearm		25 µg dissolved in 50 µL ethanol 80%	Traditional Chinese Medicine acupuncture	1 h and 20 min (initiated 20 min before intradermal capsaicin injection)	Sterile 0.30 × 30 mm needles. 8 positions in legs, arms and neck.	Sham acupuncture	1 h and 20 min (initiated 20 min before intradermal capsaicin injection)	"Fitted with a blunt tip, Streitberger placebo needles did not penetrate skin but induced a pricking sensation. By moving inside the handle, the needles shortened and thus simulated penetration when being pressed against the skin."

Table 2 (*Continued*)

Study	Induction of secondary hypersensitivity				Manipulation of secondary hypersensitivity					
					Experimental group			Control group		
	Method	Site	Duration	Dosage	Method	Duration	Dosage	Method	Duration	Dosage
Manipulation: electroacupuncture (n = 1)										
Zheng et al (2019)	Heat and topical capsaicin	Middle of forearm	Heat: 5 min Topical capsaicin: 30 min	Heat: 45 °C Capsaicin cream: 0.075%	Electroacupuncture	25 min	Sterile 0.30 × 40 mm needles. Four bilateral acupoints: "Zusanli (ST36) and Fenglong (ST40), Hegu (LI4), and Shousanli (LI10)". Frequency alternated between 5 and 15 Hz.	Sham acupuncture	25 min	"an empty plastic guide tube was tapped onto the non-acupoint, that are not along any meridians but relatively close to the real point, to produce the discernible sensation; then bent needles with adhesive bandage were taped to the dermal surface of each acupoint; and was connected to a mock electrical acupuncture stimulator without delivering electrical stimulation."
Manipulation: cognitive behavioral therapy (n = 1)										
Salomons et al (2014)	Repetitive heat stimulation	Volar forearm	28 min	45 8-second individualized intensity heat stimuli Individualized intensity: temperature started at heat pain threshold + 1 °C and slowly increased by 0.5 °C until "a tolerable temperature < 50 °C and rated ≤ 6/10 NRS on 6 consecutive trials were found".	Cognitive behavioral therapy	5 min before the heat stimuli	Focusing on "the relationship between sensory, cognitive and emotional responses to pain and were trained to reduce their stress response to the painful stimuli by identifying negative cognitions that arose and reappraising their situation to focus on potential benefits of the training (e.g. ability to cope with future pain stimuli, financial compensation). They were encouraged to use their training to cope with the painful experimental stimuli".	Sham	5 min before the heat stimuli	"Trained in interpersonal effectiveness after the heat stimuli. This training focused on managing the demands of others by effectively balancing goals and expectations and communicating assertively but respectfully with others."

Table 2 (*Continued*)

Study	Induction of secondary hypersensitivity				Manipulation of secondary hypersensitivity					
					Experimental group			Control group		
	Method	Site	Duration	Dosage	Method	Duration	Dosage	Method	Duration	Dosage
Manipulation: directing attention towards the induction (n = 1)										
Filbrich et al (2020)	High-frequency electrical stimulation	Volar forearm	5 x 1-second trains with 10-second intervals between trains	100 Hz, pulse width 2 ms, intensity 10x detection threshold to a single pulse	Vibrotactile spatial attention task		During the induction, 69 single and double vibrotactile stimulations were presented every 1 – 8 s. Participants were instructed to state when they felt double stimuli.			"[participants] were told that there would be no target vibrotactile stimuli delivered to the other [control] arm".
Manipulation: placebo analgesia (n = 1)										
Matre et al (2006)	Burn injury	Medial volar arms	5 min	46 °C	Placebo analgesia		Participants were informed that a (sham) magnet strapped on their arm next to the thermode had analgesic properties.			Participants were not informed about the (sham) magnet. They were informed that the 'metal plate' (i.e. the sham magnet) strapped on their arm next to the thermode was a thermometer.
Manipulation: spinal manipulation (n = 1)										
Mohammadian, Gonsalves et al (2004)	Topical capsaicin	Forearm	20 min	1% capsaicin, 1.5 g applied to skin	Manual spinal manipulation treatment	15 min	"short-lever, prestressed, high-velocity, low-amplitude sustained thrust and was applied at areas of vertebral subluxation in the thoracic spine."	Non-spinal manipulation treatment	15 min	"[same] manual contact and setting procedure used in the treatment but without the actual adjustment".
Manipulation: written emotional disclosure (n = 1)										
You et al (2014)	Topical capsaicin	Dominant volar forearm	30 min	6% capsaicin solution (3 g in 50 ml of 50% ethanol)	Written emotional disclosure task	20 min	"Were asked to write about the most traumatic experience of their lives".	Sham writing task	20 min	"Were asked to write about how they manage their time".

Table 2 (*Continued*)

Study	Induction of secondary hypersensitivity				Manipulation of secondary hypersensitivity					
					Experimental group			Control group		
	Method	Site	Duration	Dosage	Method	Duration	Dosage	Method	Duration	Dosage
Manipulation: negative suggestion (n = 2)										
van den Broeke et al (2014)	High-frequency electrical stimulation	Volar forearm	5 x 1-second trains with 10-second intervals between trains	100 Hz, pulse width 2 ms, intensity 20x detection threshold to a single pulse	Negative expectation		"After the HFS stimulation, your skin will become more sensitive to the pinprick stimulation'. The words 'more sensitive' were marked bold".			
Bedwell et al (2022)	High-frequency electrical stimulation	Volar forearm	5 x 1-second trains with 10-second intervals between trains	100 Hz, pulse width 2 ms, intensity 10x detection threshold to a single pulse	Manipulation of threat		(sham) skin examination and report in which participants were informed that the induction site on their volar forearm has been "approved with reservations" and they must monitor their "fragile" skin closely and there is "moderate risk of injury" during the high-frequency electrical stimulation.	No threat of tissue damage.		(sham) skin examination and report in which participants were informed that the induction site on their volar forearm has been "fully approved"; their skin is "robust" and there is "low risk of injury" during the high-frequency electrical stimulation.
Manipulation: nicotine deprivation (n = 1)										
Ditre et al (2018)	Topical capsaicin	Non-dominant volar forearm	30 min	10% capsaicin solution	Nicotine deprivation	12 to 24 h before experiment		Continued smoking		
Manipulation: sleep disruption (n = 1)										
Smith et al (2018)	Heat and topical capsaicin	Upper or lower ventral forearm	Heat: 5 min Topical capsaicin: 30 min	Heat: 45 °C Capsaicin cream: 0.35 to 0.40 g (0.1% capsaicin)	Forced awakenings	Two consecutive nights; maximum total sleep possible was 280 min.		Uninterrupted sleep	Maximum total sleep capped at 480 min	

NOTE. Studies have been grouped by manipulation method.

Outcome Measures

Twelve (of 27) studies assessed only the surface area of secondary hypersensitivity Experiments 1, 2, 3.[24,38,43–45,47,48–50,55]. Seven (of the 27) studies assessed only the magnitude of secondary hypersensitivity Experiment 2,3.[21,39,40,57,59,60] Eight (of the 27) studies assessed both the magnitude and surface area of secondary hypersensitivity.[23,41,42,51,53,54,56,58] None (of 27) studies assessed the time course of induced secondary hypersensitivity. Four (of 27) studies assessed pain elicited by the following manipulations: thermal stimulation and transcranial direct current stimulation. Seven (of 27) studies assessed adverse events.

Rescaling of Outcomes

Fifteen (of the 27) studies assessed the magnitude of secondary hypersensitivity. Of these 15, 6 used 0 to 10 rating scales with anchors of 0 = "no pain" and 10 = "worst pain imaginable" (or equivalent) to assess change in the magnitude of the secondary hypersensitivity.[23,39,51–53,60] Five (of the 15) used 0 to 100 rating scales with anchors of 0 = "no pain" and 100 = "worst pain imaginable" (or equivalent), and were rescaled to a 0 to 10 range.[40,41,56,57,61] Three (of the 15) used 0 to 100 rating scales with '50' representing the transition between non-painful (< 50) and painful (> 50) Experiment 2, 3.[21,58] The remaining study (of the 15) [54] used the −50 to +50 Sensation and pain rating scale[62] in which '0' represents the transition between non-painful (< 0) and painful (> 0). Rating data from these 3 studies were managed separately.

Risk of Bias in Included Studies

Table 3 summarizes the risk of bias results.

Selection Bias. Ten studies Experiments 2 and 3[21,45,47,48,52,54,57,58,60] were judged to be at low risk of selection bias. Fifteen studies were judged to have an unclear risk of selection bias. Of these 15, 13 failed to screen participants for both chronic and current pain Experiments 1, 2, 3[23,24,38,39–42,44,50,55,56] and 2 screened for chronic pain but failed to screen for current pain (ie, pain on the day of testing).[43,49] Two studies were judged to be at high risk of selection bias for including obviously biased samples: women with a history of trauma[51] and people who smoke > 15 cigarettes per day.[53] These biased samples were appropriate to each study's question.

Sampling Determination Bias. Six (of 27)[24,41,43,54,56,60] studies were judged to be at low risk of sampling determination bias for reporting their sample size is based on power calculations. Five studies were judged to have high risk of bias for using post hoc sampling calculations (n = 1[47]) or comparable studies (n = 4 Experiments 2 and 3[21,42,58]) in which those studies did *not* use power calculations to determine sample size. The remaining 16 (of 27) studies were judged to have an unclear risk of sampling determination bias for not reporting methods for determining sample size.

Performance Bias. Four studies[42,47,54,60] were judged to be at low risk of performance bias, for both including and reporting on the results of participants' blinding assessments. Most of the studies (20 of 27) failed to assess the effectiveness of their blinding procedure, so were judged to have an unclear risk of performance bias. The remaining 3 studies were judged to be at high risk of performance bias. Of these 3, 2 reported that blinding of participants to group allocation was not possible with studies using hyperbaric oxygen therapy,[24,43] and 1 reported that participants' blinding had been broken in 12 (out of 50) participants.[48]

Detection Bias. Only one study[54] was judged to be at low risk of detection bias for both including and reporting the results of the assessor's blinding assessment. Most studies (22 of 27) were judged to have unclear risk of detection bias for not assessing whether outcome assessors were blinded to the research question and/or whether the data analyst was blinded to group/site allocation of participants. Four studies[41,43,50,56] were judged to be at high risk of detection bias because outcome assessors and analysts were not blinded to the research question and group and/or site allocations of participants.

Veracity of Manipulation. Most (22 of the 27) studies were judged to be at low risk of manipulation veracity problems for either including manipulation checks to check the effectiveness of the manipulation (summarized in Table 4) or not needing to include a manipulation check. Seven (of the 22) did not need to include a manipulation check for transcranial direct current stimulation (n = 4), hyperbaric oxygen therapy (n = 2), or immersive 360° passive virtual reality (n = 1). The remaining 5 studies were judged to have a high risk of manipulation veracity problems. Matre, Casey (51) failed to include a manipulation check to assess participants' expectations of the placebo analgesia manipulation although the placebo was assumed to influence expectations. Mohammadian et al[44] failed to include a manipulation check to assess whether the manual spinal manipulation successfully relocated reportedly subluxed vertebrae in the thoracic spine. Rebhorn et al48 and Zheng et al[47] failed to include a manipulation check to assess whether the acupuncture, and electroacupuncture, respectively, were effective. van den Broeke et al[52] called their manipulation "negative expectation" but did not assess participants' expectations to confirm the induction of negative expectations. Hence, we refer to their manipulation as "negative suggestion" in this review.

Notably, only 1 study (of the 27) reported their manipulation as being ineffective. Bedwell et al[54] aimed to manipulate threat during the induction but their manipulation checks found no differences in self-reported pain, threat of tissue damage, or anxiety between the

Table 3. Summary of Risk of Bias Assessment

	Selection bias	Sampling determination bias	Performance bias	Detection bias	Risk of manipulation veracity problem	Attrition bias	Measurement bias SH	Measurement bias SA	Reporting bias
Baron, Wasner et al. (1999)									
Bedwell, Louw et al. (2022)									
Ditre, Zale et al. (2018)									
Filbrich, van den Broeke et al. (2020)									
Hughes, Ward et al. (2020)								N/A	
Kobor, Gal et al. (2009)								N/A	
Matre, Casey et al. (2006)							N/A		
Meeker, Keaser et al. (2019)							N/A		
Mehesz, Karoui et al. (2021)								N/A	
Mohammadian, Gonsalves et al. (2004)							N/A		
Pud, Yarnitsky et al. (2006)							N/A		
Rasmussen, Borgen et al. (2015)							N/A		
Rebhorn, Breimhorst et al. (2012)							N/A		
Salomons, Moayedi et al. (2014)							N/A		
Steyaert, Lenoir et al. (2022)									
Smith, Remeniuk et al. (2018)							N/A		
Torta, De Laurentis et al. (2020, Experiment 2)								N/A	
Torta, De Laurentis et al. (2020, Experiment 3)								N/A	
van den Broeke, Geene et al. (2014)								N/A	
Vo, Ilich et al. (2021)								N/A	
Wahl, Bidstrup et al. (2019)							N/A		
Werner, Lassen et al. (2002)									
You, Creech et al. (2014)									
Yucel, Miyazawa et al. (2001, Experiment 1)							N/A		
Yucel, Miyazawa et al. (2001, Experiment 2)							N/A		
Yucel, Miyazawa et al. (2001, Experiment 3)							N/A		
Zheng, Bai et al. (2019)							N/A		

Green = low risk of bias, red = high risk of bias, and grey = unclear risk of bias. SH = magnitude of secondary hypersensitivity. SA = surface area of secondary hypersensitivity

SH, magnitude of secondary hypersensitivity; SA, surface area of secondary hypersensitivity.
NOTE. Green = low risk of bias, red = high risk of bias, and gray = unclear risk of bias.

Table 4. Summary of Studies That Included Manipulation Checks to Assess the Effectiveness of Their Manipulation (n = 16)

STUDY	MANIPULATION	MANIPULATION CHECK
Manipulation: thermal stimulation (n = 6)		
Baron et al (1999)	Whole-body heating and cooling using a thermal suit	Temperature monitored
Pud et al (2006)	Cooling of the induction site after induction	Temperature monitored
Werner et al (2002)	Cooling of the induction site after induction	Temperature monitored
Yucel et al (2001, Experiment 1)	Heating of the induction site before and twice after induction	Temperature monitored
Yucel et al (2001, Experiment 2)	Heating of the induction site before and twice after induction	Temperature monitored
Yucel et al (2001, Experiment 3)	Heating of the induction site before and twice after induction	Temperature monitored
Manipulation: diversion of attention (n = 4)		
Kobor et al (2009)	*High* and *low* attentional load face discrimination task performed during punctate mechanical stimulation	Assessed and reported on attention during the task.
Torta et al (2020, Experiment 2)	Modified version of an N-back task performed during induction	Assessed and reported on attention during the task.
Torta et al (2020, Experiment 3)	Eriksen Flanker Task performed during induction	Assessed and reported on attention during the task.
Manipulation: cognitive behavioral therapy (n = 1)		
Salomons et al (2014)	Cognitive behavioral therapy	Pain intensity and unpleasantness during the induction.
Manipulation: directing attention towards the induction (n = 1)		
Filbrich et al (2020)	Vibrotactile spatial attention task	Assessed accuracy to detect vibrotactile stimulations and excluded participants from analysis if they "reported less than 4 vibrotactile target stimuli (out of the 8 targets) or more than 8 false alarms (ie, wrongly identified targets)".
Manipulation: written emotional disclosure (n = 1)		
You et al (2014)	Written emotional disclosure task	Self-assessment Manikin to assess emotional responses to the disclosure intervention.
Manipulation: threat manipulation (n = 1)		
Bedwell et al (2022)	Threat manipulation	Pain intensity, fear of tissue damage, and anxiety during the induction.
Manipulation: nicotine deprivation (n = 1)		
Ditre et al (2018)	Nicotine deprivation	Nicotine deprivation was verified by confirming that CO levels for < 8 parts per million or had reduced by 50% from baseline.
Manipulation: sleep disruption (n = 1)		
Smith et al (2018)	Forced awakenings	Sleep duration and disruption monitored in a controlled environment.

experimental and control group, suggesting an ineffective manipulation. Given the inefficacy of the threat manipulation, these data cannot contribute to our research question and are not reported for the review outcomes, leaving only 26 datasets contributing to data on the review outcomes.

Attrition Bias. Most studies (25 of 27) were judged to be at low risk of attrition bias for either having no withdrawals, or clearly and appropriately managing withdrawals in their statistical analyses. The remaining 2 studies[40,57] were judged to have an unclear risk of attrition bias for not reporting whether there were withdrawals from their studies.

Measurement Bias. Most studies (25 of 27) were judged to be at low risk of measurement bias. Notably, of these 25 studies, only 6 studies[41–43,47,50,54] reported that the same assessor conducted all assessments. Two studies were judged to be at a high risk of measurement bias for assessing the magnitude of secondary hypersensitivity while participants concurrently engaged in the manipulation—an attentional load task[39] and a non-interactive virtual reality arctic scene.[57] Twenty-four (of 27) studies used valid and reliable outcome measures to assess the magnitude and area of secondary hypersensitivity. The remaining 3 Experiments 2 and 3[21,58] used an unvalidated 0 to 100 rating scale, in which there were non-painful (< 50) and painful (> 50) sections.

Reporting Bias. Five (of 27) studies were judged to be at high risk of reporting bias, for either failing to report on all outcome measurements (n = 3) Experiments 1, 2, and 3[38] or failing to disclose any funding sources, conflicts of interest, or lack thereof (n = 2). Experiments 1 and 2[44,55] The remaining 22 studies were judged to be at low risk of reporting bias.

Table 5. A Summary of the Rationale for Each Manipulation and the Hypothesized and Observed Directions of the Effect of Each Manipulation on Ratings to Punctate Mechanical Stimulation and Surface Area of Secondary Hypersensitivity

	Study	Manipulation	Rationale for manipulation*	Observed direction of effect
Primary outcome: ratings to punctate mechanical stimulation				
Hypothesized to decrease ratings	Kóbor et al (2009)	Diversion of attention after induction and during the assessment	Cognitive task(s) competes with incoming nociceptive signals, reducing cognitive resources to incoming somatosensory signals.	High attentional load task: decrease Low attentional load task: no effect
	Torta et al (2019) Experiment 1	Diversion of attention during induction and before the assessment	Cognitive task(s) competes with incoming nociceptive signals, reducing cognitive resources to incoming somatosensory signals.	No effect
	Torta et al (2019) Experiment 2	Diversion of attention during induction and before the assessment	Cognitive task(s) competes with incoming nociceptive signals, reducing cognitive resources to incoming somatosensory signals.	Decrease
	Mehesz et al (2021)	Diversion of attention using immersive virtual reality after induction and during the assessment	Immersive virtual reality facilitates descending nociceptive modulatory pathways.	Decrease
	Hughes et al (2020)	Anodal transcranial direct current stimulation of M1 after induction and before the assessment	Transcranial direct current stimulation facilitates descending nociceptive modulatory pathways.	Decrease
	Meeker et al (2019)	Anodal or cathodal transcranial direct current stimulation of M1 after induction and before assessment	Transcranial direct current stimulation facilitates descending nociceptive modulatory pathways.	Anodal: decrease Cathodal: no effect
	Steyaert et al (2022)	Anodal or cathodal transcranial direct current stimulation of the DLPFC before the induction	Transcranial direct current stimulation facilitates descending nociceptive modulatory pathways.	Anodal: no effect Cathodal: no effect
	Vo et al (2021)	Anodal transcranial direct current stimulation of the 1) M1 2) DLPFC, and 3) M1 and DLPFC concurrently before the induction	Transcranial direct current stimulation facilitates descending nociceptive modulatory pathways.	M1: decrease DLPFC: decrease M1 and DLPFC: no effect
	Baron et al (1999)	Whole-body heating or cooling during induction and before the assessment	Whole-body heating facilitates low sympathetic activity, while whole-body cooling facilitates high sympathetic activity. Sympathetic activity influences peripheral nociceptive activity.	No effect of heating nor cooling
	Werner et al (2002)	Cooling of the induction site after induction and before the assessment	Cooling of the induction site is anti-inflammatory and antihyperalgesic.	No effect
	You et al (2014)	Written emotional disclosure before induction and the assessment	In the short-term, disclosure evokes distress and enhances nociceptive processing. In the long-term, disclosure facilitates cognitive processing of the traumatic event and reduces nociceptive processing.	At 4 days after the manipulation: increase At 30 days after the manipulation: decrease (in people with a history of trauma)
Hypothesized to increase ratings	Filbrich et al (2020)	Directing attention to the induction site during the induction and before the assessment	Directing attention to the induction site facilitates descending nociceptive modulatory pathways, and/or interacts with supraspinal mechanisms.	Increase
	Ditre et al (2018)	Nicotine deprivation before induction and the assessment	Nicotine deprivation facilitates release of pronociceptive neurotransmitters (e.g. glutamate, substance P, CGRP, and nitric oxide) enhancing synaptic excitability at the dorsal horn of the spinal cord.	Increase
	van den Broeke et al (2014)	Negative suggestion before induction and the assessment	Negative suggestion influences nociceptive processing via the nocebo effect.	Increase

Table 5 (*Continued*)

	Study	*Manipulation*	*Rationale for manipulation**	*Observed direction of effect*
Secondary outcome: surface area of secondary hyperalgesia				
Hypothesized to decrease the surface area of secondary hypersensitivity	Baron et al (1999)	Whole-body heating or cooling during induction and before the assessment	Whole-body heating facilitates low sympathetic activity, while whole-body cooling facilitates high sympathetic activity. Sympathetic activity influences peripheral nociceptive activity.	No effect of heating nor cooling
	Werner et al (2002)	Cooling of the induction site after induction and before the assessment	Cooling of the induction site is anti-inflammatory and antihyperalgesic.	No effect
	Pud et al (2006)	Cooling of the induction site after induction and before the assessment	Cooling of the induction site inhibits TRPV1 receptors peripherally, activates conditioned pain modulation, and activates gate control processes at the dorsal horn of the spinal cord.	Increase
	Yucel et al (2001) Experiment 1	Heating of the induction site before induction and the assessment	Heating of the induction site enhances peripheral inflammatory and afferent firing rates, thus sensitizing spinal neurons.	Data not reported and unavailable
	Yucel et al (2001) Experiment 2	Heating of the induction site before induction and the assessment	Heating of the induction site enhances peripheral inflammatory and afferent firing rates, thus sensitizing spinal neurons.	Data not reported and unavailable
	Yucel et al (2001) Experiment 3	Heating of the induction site before induction and the assessment	Heating of the induction site enhances peripheral inflammatory and afferent firing rates, thus sensitizing spinal neurons.	Data not reported and unavailable
	Meeker et al (2019)	Anodal and cathodal transcranial direct current stimulation of M1 after induction and before assessment	Transcranial direct current stimulation facilitates descending nociceptive modulatory pathways.	Anodal: decrease Cathodal: no effect
	Steyaert et al (2022)	Anodal and cathodal transcranial direct current stimulation of DLPFC before the induction	Transcranial direct current stimulation facilitates descending nociceptive modulatory pathways.	Anodal: decrease Cathodal: no effect
	Rasmussen et al (2015)	Hyperbaric oxygen therapy after induction and before assessment	Hyperbaric oxygen therapy is anti-inflammatory and antinociceptive.	Decrease
	Wahl et al (2019)	Hyperbaric oxygen therapy after induction and before assessment	Hyperbaric oxygen therapy is anti-inflammatory and antinociceptive.	Decrease
	You et al (2014)	Emotional disclosure before induction and assessment	In the short-term, disclosure evokes distress and enhances nociceptive processing. In the long-term, disclosure facilitates cognitive processing of the traumatic event and reduces nociceptive processing.	At 4 days after the manipulation: increase At 30 days after the manipulation: decrease (in people with a history of trauma)
	Salomons et al (2014)	Cognitive behavioral therapy before induction and assessment	Cognitive behavioral therapy facilitates descending nociceptive modulatory pathways.	Decrease
	Matre et al (2006)	Placebo analgesia during induction and assessment	Placebo analgesia facilitates descending nociceptive modulatory pathways.	Decrease
	Mohammadian et al (2004)	Spinal manipulation therapy after induction before assessment	Spinal manipulation therapy may activate gate control processes at the dorsal horn of the spinal cord and/or descending nociceptive modulatory pathways.	Decrease
	Rebhorn et al (2012)	Acupuncture after induction before assessment	Acupuncture facilitates the release of endorphins, descending inhibitory processes, and anti-inflammatory processes.	No effect

Table 5 (*Continued*)

	Study	Manipulation	Rationale for manipulation*	Observed direction of effect
Zheng et al (2019)	Electroacupuncture after induction before assessment	Electroacupuncture facilitates the release of endorphins.	No effect	
Filbrich et al (2020)	Directing attention to the induction site during the induction	Directing attention to the induction site facilitates descending nociceptive modulatory pathways, and/or interacts with supraspinal mechanisms.	Increase	
Ditre et al (2018)	Nicotine deprivation before induction and assessment	Nicotine deprivation facilitates release of pronociceptive neurotransmitters (e.g. glutamate, substance P, CGRP, and nitric oxide) enhancing synaptic excitability at the dorsal horn of the spinal cord.	Increase	
Smith et al (2018)	Sleep disruption before induction and assessment	Sleep disruption enhances NMDA receptor activity centrally.	Increase in male participants only No effect in female participants	

Abbreviations: M1, primary motor cortex; DLPFC, dorso-lateral prefrontal cortex; TRPV1, transient receptor potential vanilloid 1; CGRP, calcitonin gene-related peptide; NMDA, N-Methyl-D-Aspartic acid receptor.
*Kobor et al (2009) and Mohammandian et al (2004) did not specify a rationale for the manipulation. In these cases, we used published literature to generate a hypothesis about the rationale for the manipulation.
†Baron et al, Werner et al, Pud et al, Yucel et al, Rebhorn et al, Filbrich et al, and Smith et al did not specify a directional hypothesis. In these cases, we used published literature to generate a hypothesis about the direction of effect.

Primary Outcome

The Effect of Manipulation on Magnitude of Secondary Hypersensitivity (n = 14)

Fourteen (of 26) studies assessed the effect of a manipulation on the magnitude of experimentally induced secondary hypersensitivity. Table 5 summarizes the rationale for each manipulation and the hypothesized and observed directions of the effect of each manipulation on ratings to mechanical punctate stimulation, that is, the magnitude of secondary hypersensitivity.

Manipulations Hypothesized to Decrease the Magnitude of Secondary Hypersensitivity (n = 11)

Eleven (of the 14) studies used manipulations that were hypothesized to decrease the magnitude of secondary hypersensitivity: diversion of attention (n = 4), anodal transcranial direct current stimulation (n = 4), thermal stimulation (n = 2), and written emotional disclosure (n = 1). Ratings to mechanical punctate stimulation for these 11 studies are reported in Table 6.

Does Diversion of Attention Decrease the Magnitude of Secondary Hypersensitivity? (n = 4). Four studies diverted participants' attention and anticipated a decrease in the magnitude of secondary hypersensitivity. Two of these studies, both reported by Torta et al[21] (Experiments 2 and 3), had similar designs: secondary hypersensitivity was induced using low-frequency electrical stimulation to one arm while the contralateral arm served as a control for the induction. In the first experiment, participants performed an Eriksen Flanker task (ie, a cognitive loading task) during the induction (experimental condition). Torta et al[21] aimed to diminish induced secondary hypersensitivity by diverting attention to the Eriksen Flanker task. However, ratings were significantly increased after the induction compared to ratings before the induction, indicating that the manipulation did not diminish the magnitude of secondary hypersensitivity induced by low-frequency electrical stimulation. In the second experiment, participants performed a modified N-back working memory task during the induction (experimental condition). There was no significant change in ratings after the induction, suggesting that performing a modified N-back task attenuated induced secondary hypersensitivity, as assessed by magnitude. Incidentally, participants reported the N-back task to be more difficult than the Eriksen Flanker Task. A third study[63] induced secondary hypersensitivity using heat and application of topical capsaicin. After the induction, ratings to mechanical punctate stimulation were taken during 3 conditions: 1) engagement with a *high* attentional load face discrimination task (experimental condition a), 2) engagement with a *low* attentional load face discrimination task (experimental condition b), and 3) ignoring the face discrimination task (control condition). Ratings were significantly lower during the high attentional load task than during the low attentional load task or the control condition. However, there was

no significant difference in ratings between the low attentional load task and the control condition, suggesting that only high attentional load diminished ratings to mechanical punctate stimulation after induction of secondary hypersensitivity. A fourth study[57] induced secondary hypersensitivity using high-frequency electrical stimulation. After the induction, ratings to mechanical punctate stimulation were taken during an immersive 360° non-interactive virtual reality arctic scene (experimental condition) or sham virtual reality consisting of the same arctic scene displayed on a 2D monitor screen (control condition). Ratings were significantly lower during immersive virtual reality than during sham virtual reality. In summary, 3 of the 4 attention-diverting manipulations were found to diminish the magnitude of experimentally induced secondary hypersensitivity.

Does Transcranial Direct Current Stimulation Decrease the Magnitude of Secondary Hypersensitivity? (n = 4). Four studies used transcranial direct current stimulation and anticipated a decrease in secondary hypersensitivity. All 4 studies used different methods for induction and transcranial direct current stimulation. One study[64] induced secondary hypersensitivity using the application of topical capsaicin. Ten minutes after the induction ceased, either anodal transcranial direct current stimulation (experimental condition) or sham stimulation was applied over the primary motor cortex for 20 minutes at 2 separate sessions. Ratings were significantly lower after the anodal transcranial direct current stimulation than the sham stimulation. A second study[41] induced secondary hypersensitivity using heat and application of topical capsaicin while exposing participants to 20 minutes of anodal (experimental condition a), cathodal (experimental condition b), or sham (control condition) transcranial direct current stimulation applied over the primary motor cortex at 3 separate sessions. Ratings were significantly lower after anodal than sham transcranial direct current stimulation of the motor cortex. However, there was no significant difference in ratings after cathodal than sham transcranial direct current stimulation of the primary motor cortex. A third study[42] exposed participants to 20 minutes of either anodal (experimental condition a), cathodal (experimental condition b), or sham (control condition) transcranial direct current stimulation applied over the dorsolateral prefrontal cortex at 3 separate sessions. Ten minutes after the stimulation, they induced secondary hypersensitivity using high-frequency electrical stimulation. There was no significant difference in ratings after anodal compared to sham, and cathodal compared to sham transcranial direct current stimulation applied over the dorsolateral prefrontal cortex. A fourth study[60] exposed participants to 20 minutes of anodal transcranial direct current stimulation applied over the 1) primary motor cortex, 2) dorsolateral prefrontal cortex, or 3) primary motor cortex and dorsolateral prefrontal cortex concurrently (all experimental conditions), or sham stimulation at 4 separate sessions. Thereafter (time point not reported) secondary hypersensitivity was induced using low-frequency electrical stimulation. Ratings were significantly lower after transcranial direct current stimulation applied over the primary motor cortex compared to the sham stimulation and at the dorsolateral prefrontal cortex compared to the sham stimulation. There was no significant difference in ratings after concurrent stimulation of the primary motor cortex and dorsolateral prefrontal cortex compared to the sham stimulation. In summary, anodal transcranial direct current stimulation applied over the primary motor cortex was found to diminish the magnitude of experimentally induced secondary hypersensitivity. There were conflicting findings on the effect of anodal transcranial direct current stimulation applied the over dorsolateral prefrontal cortex (no effect: n = 1[42]; diminished pinprick perception: n = 1.[46] However, neither anodal transcranial direct current stimulation applied over the primary motor cortex and dorsolateral prefrontal cortex concurrently, nor cathodal transcranial direct current stimulation applied over the primary motor cortex, diminished the magnitude of experimentally induced secondary hypersensitivity.

Does Thermal Stimulation Decrease the Magnitude of Secondary Hypersensitivity? (n = 2). Two studies used thermal stimulation and anticipated a decrease in secondary hypersensitivity. Baron et al[23] induced secondary hypersensitivity using intradermal capsaicin injection while heating or cooling the whole body except the test site. There was no significant difference in ratings between whole-body heating and cooling. Werner et al[56] induced secondary hypersensitivity using a burn injury at both calves. Eight minutes after the induction ceased, one of the induction sites (experimental condition) was cooled with an 8 °C contact thermode for 30 minutes. The contralateral induction site served as the control condition. There was no significant difference in ratings between the conditions. In summary, neither of the 2 studies found thermal stimulation to diminish the magnitude of experimentally induced secondary hypersensitivity.

Does Recent Emotional Disclosure Decrease the Magnitude of Secondary Hypersensitivity? (n = 1). One study used written emotional disclosure and anticipated a decrease in secondary hypersensitivity. You et al51 recruited women who self-reported trauma (consisting of trauma at an age less than 17 years old, and recent trauma within the previous 3 years) or no trauma. All participants were randomized to engage in a writing task requiring either emotional disclosure (experimental group) or no emotional disclosure (control group). Four and 30 days after the manipulation, secondary hypersensitivity was induced using application of topical capsaicin. At both 4 and 30 days, there was no significant difference in ratings between those who engaged in the emotional disclosure task compared to those in the control group. However, in the emotional disclosure group, the magnitude of secondary hypersensitivity was significantly *greater* in participants with a history of trauma than in participants without a history of trauma. Conversely,

at 30 days, in the emotional disclosure group, the magnitude of secondary hypersensitivity was significantly *smaller* in participants with a history of trauma than in participants without a history of trauma. The authors suggest that, in people with a history of trauma, written emotional disclosure was found to increase the magnitude of experimentally induced secondary hypersensitivity at 4 days but diminish the magnitude of experimentally induced secondary hypersensitivity at 30 days after the manipulation.

Manipulations Hypothesized to Increase the Magnitude of Secondary Hypersensitivity (n = 3)

Three (of the 14) studies that assessed the magnitude of secondary hypersensitivity used manipulations that were hypothesized to increase secondary hypersensitivity: diversion of attention (n = 1), nicotine deprivation (n = 1), and negative suggestion (n = 1). Ratings to mechanical punctate stimulation for these 3 studies are reported in Table 6.

Does Directing Attention to the Induction Site Increase the Magnitude of Secondary Hypersensitivity? (n = 1). One study diverted participants' attention and anticipated an increase in the magnitude of secondary hypersensitivity. Filbrich et al[58] induced secondary hypersensitivity using high-frequency electrical stimulation simultaneously at both forearms. During the induction, participants performed a somatosensory detection task requiring them to focus their attention on one forearm (experimental site) rather than the contralateral forearm (control site). At 20 minutes after the induction, ratings were significantly greater at the experimental than at the control site. This suggests that directing attention toward the induction site during high-frequency electrical stimulation was found to increase the magnitude of experimentally induced secondary hypersensitivity.

Does Nicotine Deprivation Increase the Magnitude of Secondary Hypersensitivity? (n = 1). One study used nicotine deprivation and anticipated an increase in the magnitude of secondary hypersensitivity. Ditre et al[53] deprived a cohort of habitual smokers of nicotine for 12 to 24 hours (extended deprivation experimental group) or 2 hours (minimal deprivation experimental group b). The control group consisted of smokers who were allowed to continue smoking. The extended deprivation group was deprived of nicotine for a mean ± SD of 17 hours, 31 minutes ± 6 hours, 7 minutes. The minimal deprivation group was deprived of nicotine for a mean ± SD of 2 hours, 5 minutes ± 21 minutes. After the manipulation, secondary hypersensitivity was induced using the application of topical capsaicin. Ratings were significantly greater among the extended nicotine-deprived participants than the control group. There was no significant difference in ratings between participants in the extended deprivation group and those in the minimal deprivation group. This suggests that extended nicotine deprivation of 12 to 24 hours was found to increase the magnitude of experimentally induced secondary hypersensitivity.

Does Negative Suggestion Increase the Magnitude of Secondary Hypersensitivity? (n = 1). One study informed participants that after the induction the skin would be "more sensitive to the pinprick stimulation" and anticipated an increase in the magnitude of secondary hypersensitivity. van den Broeke et al[52] either warned participants about increased skin sensitivity from the induction (experimental group) or gave no such warning (control group). Then, secondary hypersensitivity was induced using high-frequency electrical stimulation. Ratings were significantly greater in the experimental than the control group. This suggests that the negative suggestion about the induction was found to increase the magnitude of experimentally induced secondary hypersensitivity.

Pooling of Studies

Two subgroups of manipulation were identified and considered for pooling: 1) diversion of attention (n = 4), Experiments 2 and 3,[21,39,57] and 2) transcranial direct current stimulation (n = 4, data required for meta-analysis were unavailable from one study).[40,42,60] However, there was noteworthy clinical heterogeneity among the studies that used diversion of attention (specifically, use of non-comparable rating scales), and meta-analytical pooling of those data would not add value to this review. For the studies that used transcranial direct current stimulation, we generated forest plots using the standardized mean difference, with a random effects model (Supplementary File 5).

Evidence Quality: Transcranial Direct Current Stimulation

We used the GRADE criteria to assess the quality of the evidence provided by the studies that used transcranial direct current stimulation (Table S1, Supplementary File 6). Given that 3 (of the 4) studies had an unclear risk of performance and detection bias and the remaining study had a high risk of performance and detection bias for inadequate blinding, we downgraded the risk of bias by one, indicating that there is a serious limitation in the risk of bias in this evidence base. There was no indirectness, nor was there imprecision, and results were consistent across studies (view forest plot in Supplementary File 5). Therefore, there were no downgrades for these domains. Overall, the certainty of evidence that transcranial direct current stimulation can reduce the magnitude of experimentally induced secondary hypersensitivity was scored as 'moderate', meaning that further research is likely to have an important impact on our confidence in the estimate of effect and may change the estimate.

Table 6. Ratings to Mechanical Punctate Stimulation for Manipulations Expected to Decrease or Increase the Magnitude of Secondary Hypersensitivity

Expected direction of effect	Study	Induction method	Scale	Ratings to mechanical punctate stimulation Mean ± SD, mean (SEM), or median (IQR)		Effect size
				Experimental condition	Control condition	
Decrease	Diversion of attention (n = 4)					
	Torta et al (2020) Experiment 2	Low-frequency electrical stimulation	0 to 100 rating scale with '50' representing the transition between non-painful (< 50) and painful (> 50)	27 ± 35	21 ± 35	*P*-value < .001
	Torta et al (2020) Experiment 3	Low-frequency electrical stimulation	0 to 100 rating scale with '50' representing the transition between non-painful (< 50) and painful (> 50)	25 ± 40	21 ± 30	*P*-value –.108
	Kobor et al (2009)*	Heat and topical capsaicin	0 to 10	180 g pinprick High load: 0.16 ± 0.02 Low load: 0.20 ± 0.02 300 g pinprick High load: 0.21 ± 0.03 Low load: 0.28 ± 0.02	180 g pinprick 0.25 ± 0.02 300 g pinprick 0.33 ± 0.35	High load versus low load versus single task: *P*-value =.0002
	Mehesz et al (2021)†	High-frequency electrical stimulation	0 to 100	0.72 ± 0.44	0.47 ± 0.59	*P*-value =.01
	Transcranial direct current stimulation (n = 4)					
	Hughes et al (2020)‡	Topical capsaicin	0 to 100	Anodal: 0.55 {0.1}	Sham anodal: 1.1 {0.3}	*P*-value < .05
	Meeker et al (2019)§	Heat and topical capsaicin	0 to 100	Anodal: 5 ± 3 Cathodal: 3 ± 2	Sham anodal: 1 ± 3 Sham cathodal: 1 ± 3	Anodal: *P*-value =.02 Cathodal: not reported
	Steyaert et al (2022)	High-frequency electrical stimulation	0 to 10	Anodal at DLPFC: 6.1 ± 1.21 Cathodal DLPFC: 6.0 ± 1.21	Sham anodal at DLPFC: 6.4 ± 1.41 Sham cathodal DLPFC: 6.4 ± 1.41	Anodal: not reported Cathodal: not reported
	Vo et al (2021)	Low-frequency electrical stimulation	0 to 10	Anodal at DLPFC: 1.6 ± 2.50 Anodal at M1: 1.6 ± 2.50 Anodal at M1 and DLPFC concurrently: 1.9 ± 2.50	Sham anodal at DLPFC: 2.1 ± 2.50 Sham anodal at M1: 2.1 ± 2.50 Sham anodal at M1 and DLPFC concurrently: 2.1 ± 2.50	
	Thermal stimulation (n = 2)					
	Baron et al (1999)	Intradermal capsaicin injection	0 to 10	3.2 ± 0.5	3.4 ± 0.7	Not reported
	Werner et al (2002)	Burn injury	0 to 100	15 (22)	20 (25)	*P*-value > .5

Table 6 (*Continued*)

Expected direction of effect	*Study*	*Induction method*	*Scale*	*Ratings to mechanical punctate stimulation Mean ± SD, mean (SEM), or median (IQR)*		
				Experimental condition	*Control condition*	*Effect size*
Emotional disclosure (n = 1)						
Topical capsaicin	0 to 10	4 days: With history of trauma: 2.6 ± 0.6 No trauma: 1.3 ± 0.1 30 days: With history of trauma: 1.0 ± 0.6 No trauma: 2.0 ± 0.7	4 days: With history of trauma: 2.0 ± 0.8 No trauma: 2.1 ± 0.6 30 days: With history of trauma: 1.7 ± 1.0 No trauma: 1.1 ± 0.6	4 days: In experimental group trauma versus no trauma: *P*-value < .025 30 days: In experimental group trauma versus no trauma: *P*-value < .025		
Increase	Directing attention to the induction site (n = 1)					
	Filbrich et al (2020)	High-frequency electrical stimulation	0 to 100 rating scale with '50' representing the transition between non-painful (< 50) and painful (> 50)	50 ± 16	45 ± 25	*P*-value = .003
	Nicotine deprivation (n = 1)					
	Ditre et al (2018)**	Topical capsaicin	0 to 10	Extended deprivation: 20.84 ± 18.12 Minimal deprivation: 15.52 ± 17.21	10.87 ± 9.14	*P*-value < .05 Not reported
	Negative suggestion (n = 1)					
	van den Broeke et al (2014)	High-frequency electrical stimulation	0 to 10	38 ± 17	23 ± 17	Not reported

Abbreviations: M1, primary motor cortex, DLPFC, dorso-lateral prefrontal cortex.
*Mechanical punctate stimulation ratings scored on a 0 to 10 sliding scale were converted to discrete digital values and normalized to (and reported here as) a range of 0 to 1.
†Mechanical punctate stimulation was log transformed and converted to (and reported here as) z-scores.
‡Mechanical punctate stimulation ratings were calculated and reported as area under the response curve for the ratio of post-manipulation/pre-manipulation.
§Mechanical punctate stimulation ratings were converted (and reported here as) a change in (ie, delta scores) mechanical punctate stimulation.
**Rating to mechanical punctate stimulation was calculated and reported as area under the response curve.

Secondary Outcomes

The Effect of Manipulation on Area of Secondary Hypersensitivity (n = 19)

Nineteen (of the 26) studies assessed the effect of manipulation on the surface area of secondary hypersensitivity. Table 5 summarizes the rationale for each manipulation and the hypothesized and observed directions of the effects of each manipulation on the area of secondary hypersensitivity.

Manipulations Hypothesized to Decrease the Area of Secondary Hypersensitivity (n = 16)

Sixteen (of 19) studies that assessed surface area of secondary hypersensitivity used manipulations hypothesized to decrease the area of secondary hypersensitivity: thermal stimulation (n = 6), transcranial direct current stimulation (n = 2), hyperbaric oxygen therapy (n = 2), written emotional disclosure (n = 1), cognitive behavioral therapy (n = 1), placebo analgesia (n = 10), spinal manipulation therapy (n = 1), acupuncture (n = 1), and electroacupuncture (n = 1). The area of secondary hypersensitivity for these 20 studies are reported in Table 7.

Does Thermal Stimulation Decrease the Area of Secondary Hypersensitivity?(n = 6). Six studies used thermal stimulation and anticipated a decrease in the surface area of secondary hypersensitivity. For 3 of the studies, all reported by Yucel et al[38] we were unable to obtain the data; however, they reported no significant difference in the area of secondary hypersensitivity after thermal stimulation for all 3 studies. A fourth study[23] induced secondary hypersensitivity using intradermal capsaicin injection while heating or cooling the whole body except the test site. There was no significant difference in the area of secondary hypersensitivity after whole body heating than after cooling. A fifth study[56] induced secondary hypersensitivity using a burn injury at both calves. Eight minutes after the induction ceased, one of the induction sites (experimental condition) was cooled with an 8 °C contact thermode for 30 minutes. The contralateral induction site served as the control condition. There was no significant difference in the area of secondary hypersensitivity between the conditions. A sixth study[55] induced secondary hypersensitivity using intradermal capsaicin injection. Eight minutes after the induction, the induction site was exposed to 30-second trials of contact cooling with a thermode at 20 °C, 10 °C, or 0 °C (randomized order). The area of secondary hypersensitivity was significantly *larger* after cooling than before cooling. In summary, none of the 6 studies found thermal stimulation to diminish the area of experimentally induced secondary hypersensitivity; however, no data were provided to support the conclusion for 3 (of the 6 studies) Experiments 1, 2, and 3.[38] Additionally, 1 (of the 6) found an unexpected increase in the area of experimentally induced secondary hypersensitivity after cold stimulation.

Does Transcranial Direct Current Stimulation Decrease the Surface Area of Secondary Hypersensitivity? (n = 2). Two studies used transcranial direct current stimulation and anticipated a decrease in the surface area of secondary hypersensitivity. In one study,[41] induced secondary hypersensitivity using heat and application of topical capsaicin while exposing participants to 20 minutes of anodal (experimental condition a), cathodal (experimental condition b), or sham (control condition) transcranial direct current stimulation applied over the primary motor cortex, at 3 separate sessions. The area of secondary hypersensitivity was significantly smaller after anodal than after cathodal transcranial direct current stimulation of the primary motor cortex. However, there was no significant difference in the area of secondary hypersensitivity after anodal than sham transcranial direct current stimulation of the motor cortex. A second study[42] exposed participants to 20 minutes of anodal (experimental condition a), cathodal (experimental condition b) or sham transcranial direct current stimulation applied over the dorsolateral prefrontal cortex at 3 separate sessions. Ten minutes after the stimulation, secondary hypersensitivity was induced using high-frequency electrical stimulation. There was no significant difference in the area of secondary hypersensitivity after anodal than sham, or cathodal than sham transcranial direct current stimulation applied over the dorsolateral prefrontal cortex. In summary, anodal transcranial direct current stimulation applied over the primary cortex or dorsolateral prefrontal cortex was found to diminish the area of experimentally induced secondary hypersensitivity in 1 study. However, cathodal transcranial direct current stimulation applied over the primary cortex or dorsolateral prefrontal cortex did not diminish the area of experimentally induced secondary hypersensitivity in 2 studies.

Does Hyperbaric Oxygen Therapy Decrease the Surface Area of Secondary Hypersensitivity? (n = 2). Two studies used hyperbaric oxygen therapy and anticipated a decrease in the surface area of secondary hypersensitivity. Both studies[24,43] induced secondary hypersensitivity using a burn injury. Then, participants were exposed to 90 minutes hyperbaric oxygen therapy (2.4 atmospheric pressure, 100% O_2; experimental condition) or ambient pressure at room air (1 atmospheric pressure, 21% O_2; control condition). In both studies, the area of secondary hypersensitivity was significantly smaller after hyperbaric oxygen therapy than the control condition. Therefore, hyperbaric oxygen therapy was found to diminish the area of experimentally induced secondary hypersensitivity.

Does Acupuncture or Electroacupuncture Decrease the Surface Area of Secondary

Table 7. Surface Area of Secondary Hypersensitivity for Manipulations That Expected to Decrease or Increase the Surface Area of Secondary Hypersensitivity (n = 16)

Expected direction of effect	Study	Induction method	Surface area of secondary hypersensitivity (cm^2) Mean ± SD, mean (SEM), or median (IQR)		Effect size
			Experimental condition	Control condition	
Decrease	Thermal stimulation (n = 6)				
	Yucel et al (2001) Experiment 1	Topical capsaicin	Data not reported and unavailable	Data not reported and unavailable	Not reported
	Yucel et al (2001) Experiment 2	Intradermal capsaicin injection	Data not reported and unavailable	Data not reported and unavailable	Not reported
	Yucel et al (2001) Experiment 3	Burn injury	Data not reported and unavailable	Data not reported and unavailable	Not reported
	Baron et al (1999)	Intradermal capsaicin injection	88 ± 13	86 ± 13	Not reported
	Werner et al (2002)	Burn injury	45 (40)	61 (47)	*P*-value > .4
	Pud et al (2006)	Intradermal capsaicin injection	11.4 (1.72)	10 (1)	Not reported
	Transcranial direct current stimulation (n = 2)				
	Meeker et al (2019)	Heat and topical capsaicin	Anodal at M1: 21 ± 5 Cathodal at M1: 12 ± 6	Sham anodal at M1: 6 ± 12 Sham cathodal at M1: 6 ± 12	Anodal: not reported Cathodal: not reported Anodal vs cathodal: *P*-value =.075
	Steyaert et al (2022)	High-frequency electrical stimulation	Anodal at DLPFC: 73 ± 48 Cathodal at DLPFC: 73 ± 52	Sham anodal at DLPFC: 79 ± 48 Sham cathodal at DLPFC: 79 ± 48	Anodal: not reported Cathodal: not reported
	Hyperbaric oxygen therapy (n = 2)				
	Rasmussen et al (2015)	Burn injury	34.6 (22.9–39.8)	42.0 (31.1–71.4)	*P*-value =.011
	Wahl, Bidstrup et al (2019)	Burn injury	18.8 (10.5–27.0)	32.0 (20.1–43.9)	*P*-value –.021
	Acupuncture (n = 1)				
	Rebhorn et al (2012)*	Intradermal capsaicin injection	92	90	Not reported
	Electroacupuncture (n = 1)				
	Zheng et al (2019)	Heat and topical capsaicin	47 {6}	50 (5)	*P*-value =.948
	Emotional disclosure (n = 1)				
	You et al (2014)	Topical capsaicin	4 days: With history of trauma: 130 {60} No trauma: 70 (23) 30 days: With history of trauma: 40 (30)No trauma: 100 (60)	4 days: With history of trauma: 65 (33) No trauma: 70 (22) 30 days: With history of trauma: 90 (60) No trauma: 45 (50)	4 days: With trauma experimental versus control groups: *P*-value < .05 In experimental group trauma versus no trauma: *P*-value < .025 30 days: In experimental group trauma versus no trauma: *P*-value < .025 With trauma experimental versus control groups: *P*-value < .05
	Cognitive behavioral therapy (n = 1)				
	Salomons et al (2014)	Burn injury	Session 1: 48 (7.01) Session 8: 29.8 (7.31)	Session 1: 45 (6.29) Session 8: 48 (8.80)	Experimental group: Session 1 versus 8: *P*-value < .01 Control group: Session 1 versus 8: *P*-value =.65

Table 7 (*Continued*)

			Surface area of secondary hypersensitivity (cm^2) *Mean ± SD, mean (SEM), or median (IQR)*		
Expected direction of effect	*Study*	*Induction method*	*Experimental condition*	*Control condition*	*Effect size*
Placebo analgesia (n = 1)					
Burn injury	Session 1: 65 (90) Session 2: 65 (75) Session 3: 45 (80)	Session 1: 50 (95) Session 2: 50 (150) Session 3: 50 (100)	Comparison between experimental and control group Session 1: not reported Session 2: not reported Session 3: not reported Comparison within experimental group Session 2 versus 3: *P*-value =.002		
Spinal manipulation therapy (n = 1)					
Mohammadian, Gonsalves et al (2004)	Topical capsaicin	27 (4)	45 (10)	*P*-value =.007	
Increase	Directing attention to the induction site (n = 1)				
	Filbrich et al (2020)	High-frequency electrical stimulation	Proximal-distal: 69 ± 67[†] Lateral-medial: 33 ± 41[†]	Proximal-distal: 60 ± 67[†] Lateral-medial: 20 ± 32[†]	*P*-value –.206 *P*-value < .001
	Nicotine deprivation (n = 1)				
	Ditre et al (2018)	Topical capsaicin	Extended deprivation: 71.98 ± 55.17 Minimal deprivation: 60.95 ± 56.78	45.07 ± 37.14	*P*-value < .05 Not reported
	Sleep disruption (n = 1)				
	Smith et al (2018)	Topical capsaicin	Male: 18 ± 5.0[‡] Female: 12.5 ± 4.5[‡]	Male: 11.5 ± 5.0[‡] Female: 15.5 ± 4.5[‡]	*P*-value =.008 *P*-value =.332

[*]Data presented as mean (SEM); however, it was not possible to accurately read the SEM off the plot.
[†]Surface area reported (and presented here) in mm.
[‡]Surface area reported in mm^2, converted (and reported here) to cm^2.

Hypersensitivity? (n = 1 each). One study used acupuncture and anticipated a decrease in the surface area of secondary hypersensitivity. Rebhorn et al[48] induced secondary hypersensitivity using intradermal capsaicin injection and then exposed participants to either traditional Chinese Medicine acupuncture (experimental group) or sham acupuncture (control group). There was no significant difference in the area of secondary hypersensitivity between groups. Zheng et al[47] induced secondary hypersensitivity using heat and application of topical capsaicin and then exposed participants to 30 minutes of either electroacupuncture (experimental group) or sham electroacupuncture (control group). There was no significant difference in the area of secondary hypersensitivity between groups. In summary, neither acupuncture nor electroacupuncture was found to diminish the area of experimentally induced secondary hypersensitivity.

Does Recent Emotional Disclosure Decrease the Surface Area of Secondary Hypersensitivity? (n = 1). One study used written emotional disclosure and anticipated a decrease in the surface area of secondary hypersensitivity. You et al[51] recruited women who self-reported trauma (consisting of trauma at an age less than 17 years old, and recent trauma within the previous 3 years) or no trauma. All participants were randomized to engage in a writing task requiring either emotional disclosure (experimental group) or no emotional disclosure (control group). Four and 30 days after the manipulation, secondary hypersensitivity was induced using the application of topical capsaicin. At 4 days, in participants with a history of trauma, the area of secondary hypersensitivity was significantly *larger* in the emotional disclosure group than in the control group. Additionally, in the emotional disclosure group, the area of secondary hypersensitivity was significantly *larger* in participants with a history of trauma than in participants without a history of trauma. There was no significant between-group difference for participants with no trauma. Conversely, at 30 days, in participants with a history of trauma, the area of secondary hypersensitivity was significantly *smaller* in the emotional disclosure group than in the control group. Additionally, in the emotional disclosure group, the area of secondary hypersensitivity was significantly *smaller* in participants with a history of trauma than in participants without a history of trauma. Again, there was no significant between-group difference for participants with no trauma. This suggests that, in people with a history of trauma, written emotional disclosure was found to increase the area of experimentally induced secondary hypersensitivity at 4 days but diminish the area of experimentally induced secondary hypersensitivity 30 days after the manipulation.

Does Cognitive Behavioral Therapy Decrease the Surface Area of Secondary Hypersensitivity? (n = 1). One study used cognitive behavioral therapy and anticipated a decrease in the surface area of secondary hypersensitivity. During 8 sessions, Salomons et al[49] trained participants in either 5 minutes of cognitive behavioral therapy which was focused on reducing participants' negative thoughts and emotions towards painful stimuli (experimental group) or 5 minutes of interpersonal effectiveness training which was focused on managing demands and expectations of others (control group). At each session, after the 5 minutes of training in cognitive behavioral therapy, participants were exposed to brief thermal stimulations. The area of secondary hypersensitivity was assessed at the first and last (8th) sessions only. At the last session, the area of secondary hypersensitivity was significantly smaller in participants who received cognitive behavioral therapy than in the control group. This suggests that repeated sessions of cognitive behavioral therapy was found to diminish the area of experimentally induced secondary hypersensitivity.

Does Placebo Analgesia Decrease the Surface Area of Secondary Hypersensitivity? (n = 1). One study used placebo analgesia and anticipated a decrease in the surface area of secondary hypersensitivity. Participants were informed either that "the aim of the study was to test the analgesic effectiveness of a magnet against heat pain" (experimental group) or that "the aim of the study was to investigate hypersensitivity of the skin after a heat stimulus" (control group). Secondary hypersensitivity was induced at 3 sessions, separated by 4 to 7 days, using a burn injury to 1 arm. The magnet (ie, placebo analgesia) was attached to the arm during the induction at the third session only. At the third session, the area of secondary hypersensitivity was significantly smaller in participants who received the induction in the presence of the magnet, that is, placebo analgesia than in the control group. Additionally, in participants in the experimental group, the area of secondary hypersensitivity was significantly smaller at the third session when the magnet, that is, placebo analgesia was present than the second session when the magnet was absent. This suggests that placebo analgesia was found to diminish the area of experimentally induced secondary hypersensitivity.

Does Spinal Manipulation Therapy Decrease the Surface Area of Secondary Hypersensitivity? (n = 1). One study used spinal manipulation and anticipated a decrease in the surface area of secondary hypersensitivity. Mohammadian et al[44] induced secondary hypersensitivity using topical capsaicin. Approximately 10 minutes after the removal of the capsaicin cream, participants were exposed to either 15 minutes of manual spinal manipulation applied to relocate thoracic vertebrae that were deemed to have subluxed (experimental condition) or non-spinal manipulation (control condition). The area of secondary hypersensitivity was significantly smaller after the spinal manipulation than the control condition. This suggests that spinal manipulation was found to diminish the area of experimentally induced secondary hypersensitivity.

In summary, anodal transcranial direct current stimulation (n = 2), hyperbaric oxygen therapy (n = 2), written emotional disclosure (n = 1; only in participants

with history of trauma), cognitive behavioral therapy (n = 1), placebo analgesia (n = 1), and spinal manipulation therapy (n = 1) were found to diminish the surface area of secondary hypersensitivity. Conversely, none of thermal stimulation (n = 3), acupuncture (n = 1), nor electroacupuncture (n = 1) diminished the surface area of secondary hypersensitivity. Four studies failed to report their results, and one study reported an unexpected increase in the surface area of secondary hypersensitivity after cold thermal stimulation.

Manipulations Hypothesized to Increase the Area of Secondary Hypersensitivity (n = 3). Three (of 20) studies that assessed surface area used manipulations hypothesized to increase the surface area of secondary hypersensitivity: diversion of attention (n = 1), nicotine deprivation (n = 1), and sleep deprivation (n = 1). The area of secondary hypersensitivity for these 3 studies is reported in Table 7.

Does Directing Attention to the Induction Site Increase the Surface Area of Secondary Hypersensitivity?(n = 1). One study diverted participants' attention and anticipated an increase in the surface area of secondary hypersensitivity. Filbrich et al[58] induced secondary hypersensitivity using high-frequency electrical stimulation simultaneously at both forearms. During the induction, participants performed a somatosensory detection task requiring them to focus their attention on one forearm (experimental site) rather than the contralateral forearm (control site). Along the medial-lateral axis, the area of secondary hypersensitivity was larger at the experimental site than the control. However, along the proximal-distal axis, there was no significant difference in the area of secondary hypersensitivity between the sites. This suggests that directing attention towards the induction site during high-frequency electrical stimulation was found to increase the area of secondary hypersensitivity along the medial-lateral axis.

Does Nicotine Deprivation Increase the Surface Area of Secondary Hypersensitivity? (n = 1). One study used nicotine deprivation and anticipated an increase in the surface area of secondary hypersensitivity. Ditre, Zale (54) deprived a cohort of habitual smokers of nicotine for 12 to 24 hours (extended deprivation experimental group) or 2 hours (minimal deprivation experimental group b). The control group consisted of smokers who were allowed to continue smoking. The extended deprivation group was deprived of nicotine for a mean ± SD of 17 hours, 31 minutes ± 6 hours, 7 minutes. The minimal deprivation group was deprived of nicotine for a mean ± SD of 2 hours, 5 minutes ± 21 minutes. After the manipulation, secondary hypersensitivity was induced using the application of topical capsaicin. The area of secondary hypersensitivity was significantly larger among the extended nicotine-deprived participants than the control group. There was no significant difference in the area of secondary hypersensitivity between participants in the extended deprivation group and those in the minimal deprivation group. This suggests that nicotine deprivation of 12 to 24 hours among smokers was found to increase the area of experimentally induce secondary hypersensitivity.

Does Sleep Disruption Increase the Surface Area of Secondary Hypersensitivity? (n = 1). One study used sleep disruption and anticipated an increase in the area of secondary hypersensitivity. Smith, Remeniuk (46) exposed participants to 2 consecutive nights of sleep disruption (experimental group) or 2 nights of undisturbed sleep (control group). Thereafter, secondary hypersensitivity was induced using the application of topical capsaicin. In males only (n = 33), the area of secondary hypersensitivity was significantly larger after sleep disruption than after undisturbed sleep. However, this effect was not seen in female participants (n = 46). This suggests that sleep disruption was found to increase the area of experimentally induce secondary hypersensitivity in male participants.

Pooling of Studies

Three subgroups of manipulation were considered for pooling: 1) thermal stimulation (n = 6) Experiments 1, 2, and 3,[23,38,55,56] 2) transcranial direct current stimulation (n = 2),[41,42] and 3) hyperbaric oxygen therapy (n = 2).[24,43] However, the data required for meta-analysis were unavailable from 3 of the 6 studies that used thermal stimulation, and 1 of the 2 studies that used transcranial direct current stimulation. Therefore, it was only feasible to pool data from the 2 studies that used hyperbaric oxygen therapy. It was not appropriate for any other studies to be pooled given the high heterogeneity in the manipulation procedures. We generated forest plots using the standardized mean difference, with a random effects model (Supplementary File 7).

Assessment of the Quality of Body of Evidence

We used the GRADE criteria to assess the quality of the evidence provided by the studies that used hyperbaric oxygen therapy for (Table S2, Supplementary File 6). Given that both had a high risk of performance and detection bias for inadequate blinding, we downgraded the risk of bias by one, indicating that there is a serious limitation in the risk of bias in this evidence base. There was no indirectness nor were there imprecision, and results were consistent across studies (view forest plot in Supplementary File 7). Therefore, there were no downgrades for those domains. Overall, the certainty of evidence that hyperbaric oxygen therapy can reduce the surface area of experimentally induced secondary hypersensitivity was scored as 'low'—meaning that further research is very likely to have an important impact on our confidence in the estimate of effect and is likely to change the

estimate—because of the serious limitations in the risk of bias and the small total sample of 36 participants.

Time Course of Secondary Hypersensitivity

No study directly reported the time to resolution of secondary hypersensitivity. However, 7 (of 14) studies Experiments 2 and 3[21,42,43,46,52,56,58] that assessed the magnitude of secondary hypersensitivity plotted ratings to mechanical punctate stimulation over time and 5 (of 19) studies [42,43,47,55,56] that assessed the surface area of secondary hypersensitivity plotted the surface area over time in a way that allows for direct visual comparison between experimental and control groups. For magnitude of secondary hypersensitivity, 6 (of the 7) showed no visually obvious group differences in the development of secondary hypersensitivity. The remaining study[58] showed a more rapid development of secondary hypersensitivity in the experimental than in the control group. For surface area of secondary hypersensitivity, 3 (of 5) showed no visually obvious group differences in the development of secondary hypersensitivity. The remaining 2 studies[43,55] showed a more rapid development of secondary hypersensitivity in the experimental than in the control condition, in other words the surface area of secondary hypersensitivity developed to a higher peak in the experimental than control condition, resulting in a steeper slope.

Pain (n = 4) and Other Adverse events (n = 7) Associated With the Manipulations

Four (of 27) studies assessed pain during manipulation procedures, of which 2 used localized application of a cold contact thermode[55,56] and 2 used transcranial direct current stimulation.[61,65] Both studies using a cold contact thermode took ratings on a 0 to 100 scale and provided data on 4 different cold temperatures. The mean ± SD/(range) ratings were: for a 20 °C stimulus: 9.1 ± 0.9[55]; for a 10 °C stimulus: 7.9 ± 0.9[55]; for an 8 °C stimulus: 0 (0–1)[56]; for a 0 °C stimulus: 15.1 ± 1.3.[55] Notably, although Pud, Yarnitsky et al (2006) refer to the 20 °C stimulus as a *painful* stimulus, a 20 °C stimulus is not noxious and is unlikely to be perceived as painful. In the 2 studies using transcranial direct current stimulation, one study[42] reported headache (anodal: n = 4 of 18, cathodal: n = 3 of 18; and sham: n = 4 of 18) and neck pain (anodal: n = 4 of 18, cathodal: n = 2 of 18; and sham: n = 3 of 18), while the other study[46] reported no significant differences in headache and neck pain after anodal than after sham transcranial direct current stimulation.

Seven (of 27) studies[24,41,47,53,60,61] assessed other adverse events to the manipulation. Three (of the 7) reported no adverse events, to hyperbaric oxygen therapy (n = 2) or electroacupuncture (n = 1). A fourth study[41] assessed but did not report on adverse events of the transcranial direct current stimulation manipulation. A fifth study[53] assessed self-reported symptoms of nicotine withdrawal using the Minnesota Nicotine Withdrawal Scale[66] and found no significant difference in the scores between groups. Further, the scores were relatively low, indicating minimal self-reported symptoms of nicotine withdrawal. The remaining 2 (of the 7) studies used transcranial direct current stimulation. One[42] reported blurred vision (anodal: n = 1 of 18; cathodal: n = 1 of 18), scalp irritation (anodal: n = 3 of 18; cathodal: n = 3 of 18), tingling (anodal: n = 3 of 18; cathodal: n = 1 of 18; sham: n = 1 of 18), itching (anodal: n = 3 of 18; cathodal: n = 1 of 18; sham: n = 1 of 18), and burning sensation (anodal: n = 3 of 18; cathodal: n = 3 of 18; sham: n = 1 of 18) after transcranial direct current stimulation. The other[60] reported significantly more itching, tingling, and burning sensation during anodal transcranial direct current stimulation over the primary motor and dorso-lateral prefrontal cortices concurrently than over each cortex separately. It also reported more heat and discomfort during anodal transcranial direct current stimulation over the primary motor and dorso-lateral prefrontal cortices concurrently or only over the primary motor than over only the dorso-lateral prefrontal cortex. Overall, hyperbaric oxygen therapy, electroacupuncture, or nicotine withdrawal were associated with no adverse events, whereas transcranial direct current stimulation was associated with blurred vision, scalp irritation, tingling, itching, and burning sensation.

Publication Bias

Although we initially planned and stated in the protocol that we would assess publication bias with the use of funnel plots, given the small sample size and high methodological heterogeneity, we believed that funnel plots would not add value.

Discussion

The aim of this systematic review and meta-analysis was to understand the influence of non-pharmacological manipulations on experimentally induced secondary hypersensitivity in adult humans without clinical pain. We identified 27 eligible studies that used non-pharmacological manipulations expected to influence the magnitude (primary review outcome) and/or surface area (secondary review outcome) of secondary hypersensitivity. As explained in the *Veracity of manipulation* section, one study[54] reported their threat manipulation to be ineffective; therefore, their data were not useful for answering the research question and were not reported for the review outcomes. We reported on a total of 26 datasets.

Manipulations of Attention

Engagement in a more cognitively demanding task had a stronger effect on the pinprick perception in the secondary zone than engagement in a less demanding task. This was shown in 2 studies, across tasks that either loaded working memory[21] or required discrimination between faces.[39] The influence of cognitive loading on

pain may reflect cognitive tasks competing with incoming nociceptive signals, reducing cognitive resources to incoming somatosensory signals.[21,67] Indeed, the cortical areas activated by cognitively demanding tasks overlap with those associated with pain processing, including the anterior cingulate, dorso-lateral prefrontal, and posterior parietal cortices.[68–72] However, a recent study[73] tried to replicate the findings of Torta et al[21] but instead found that the same high cognitive load task did not prevent the development of secondary hypersensitivity.

Another insight from the 6 datasets on manipulations of attention is that diverting attention *away* from the induction *diminished* the magnitude of secondary hypersensitivity (1 study[21]), whereas diverting attention *toward* the induction site *increased* the magnitude of secondary hypersensitivity (1 study[58]). These results add to a separate body of evidence that attention is closely associated with reported pain severity: focusing attention away from a painful stimulus is linked to decreased pain severity,[67,74–78] whereas focusing attention toward a painful stimulus is linked to increased pain severity.[75] That evidence is mostly based on the brief thermal or electrical painful stimuli instead of experimental secondary hypersensitivity. However, partial reinforcement of this principle is provided by 3 (of 6) datasets in the current review that manipulated attention *during* mechanical punctate stimulation *sensory testing* (ie, brief painful stimuli): two found that diverting attention during mechanical punctate stimulation diminished the magnitude of secondary hypersensitivity. Conversely, a recent study[79] tried to replicate the findings of Filbrich, van den Broeke (59) but instead found that diverting attention towards the induction site had no effect on the magnitude of secondary hypersensitivity. The contradictory findings in these 2 replication studies [73,79] cast doubt on the potency of manipulations of attention in influencing experimentally induced secondary hypersensitivity.

One caveat, when interpreting findings on manipulating attention, is the high risk of measurement bias in the 3 datasets that engaged participants in a cognitive loading task *during* mechanical punctate stimulation (the other 3 studies applied the manipulation of attention during the induction and *not* during mechanical punctate stimulation). During mechanical punctate stimulation, some participants might direct their attention *towards* the painful stimulus to give a meaningful rating, thus breaking engagement in the cognitive loading task and presumably reducing the effect of the manipulation. Other participants might direct attention *away* from the painful stimulus and towards the cognitive loading task as instructed, compromising the validity of the ratings. None of these studies presented data to identify which strategy (ies) their participants used. Other studies have suggested that certain individuals are more likely to focus on a painful stimulus than a cognitive loading task, and vice versa, when the 2 requirements are applied concurrently,[72] and that the drivers of this focus may reflect pain coping strategies or resilience.[68] However, it is not currently possible to predict these strategies at the individual level. Therefore, the results from the studies that did not manipulate attention during mechanical punctate stimulation are likely stronger than those that manipulated attention during mechanical punctate stimulation.

Consistency of Findings Across Indicators of Secondary Hypersensitivity

Eight (of 26) studies assessed the influence of a manipulation on both magnitude *and* surface area of secondary hypersensitivity, allowing an exploration of the consistency of effects across both indicators of secondary hypersensitivity. In 7 (of 8) studies, effects were consistent for nicotine deprivation (n = 1; increase in outcomes), directing attention toward the induction site (n = 1; increase in outcomes), anodal transcranial direct current stimulation over the primary motor cortex (n = 2; decrease in outcomes), emotional disclosure (n = 1; increase in outcomes at 4 days; decrease at 30 days), and thermal stimulation (n = 2; no effect on outcomes). In one study,[42] effects were inconsistent: anodal transcranial direct current stimulation over the dorsolateral prefrontal cortex had no effect on the magnitude, but decreased the area of secondary hypersensitivity. Notably, this consistency of effect across both indicators of secondary hypersensitivity is reported at a group-level. However, intraindividual variability in pain outcomes is well known in both clinical and experimental work and could provide further insight into the effects of interventions; however, given raw data are seldom presented, intraindividual variability is frequently not reported and overlooked.[80]

Opportunities to Improve the Body of Evidence

The current review identified 4 methodological strategies that have the potential to improve the quality of evidence on this topic: 1) manipulation checks, 2) structured strategies to achieve and verify blinding of participants, assessors, and analysts, 3) control conditions or control time points to confirm the effectiveness of the induction procedure, and 4) public sharing of raw data.

Five (of 27) studies failed to include manipulation checks to verify the effect of their manipulation on the putative target. Failing to confirm the efficacy of the manipulation itself on the putative target reduces clarity when trying to interpret the effect of manipulating the target on experimentally induced secondary hypersensitivity. Given the lack of manipulation checks, it is possible that this review draws conclusions based on ineffective manipulations, that is, the target was not actually manipulated, in which case the concluded effect of the manipulation on secondary hypersensitivity may be inaccurate. Specifically, 4 (of these 5) studies [41,44,47,52] found their manipulation influenced secondary hypersensitivity. However, without manipulation checks to verify the effect of their manipulation on the putative

target, we cannot be certain whether this effect was due to a change in the putative target or something else entirely. One study[48] found the manipulation to have no effect on secondary hypersensitivity, which could either be because the manipulation failed to influence the putative target or because manipulating the target did not influence secondary hypersensitivity. In contrast, the inclusion of a manipulation check in the only study from which we did not include the outcomes data[54] facilitated clarity about this: the manipulation check showed no effect of the manipulation on the putative target, therefore no effects on secondary hypersensitivity could reasonably be anticipated, so we excluded the data. Including manipulation checks to verify the effect of their manipulation on the putative target will foster clarity when interpreting results in future studies.

Five (of 27) studies failed to include structured strategies to both achieve and verify the blinding of participants, assessors, and analysts. Further, only 2 (of 27) studies assessed if blinding was upheld among participants and researchers. This opened studies up to unclear and high risks of performance and detection bias. Structured strategies to both achieve and verify blinding will improve methodological rigor by reducing the risk of performance and detection bias, increasing the reliability of the results.

Twelve (of 27) studies included a control condition or time point to confirm the effectiveness of the *induction* procedure. Including a control for the induction clarifies that secondary hypersensitivity was indeed induced. Although experimentally induced secondary hypersensitivity is an established model, the different induction methods have variable effects in different individuals.[81] Two (of 27) studies using placebo analgesia and transcranial direct current stimulation recruited an enriched sample comprising participants who had previously developed secondary hypersensitivity after experimental induction.[41,50] One of these studies[50] also excluded participants who showed >25% inter-session variability in secondary hypersensitivity at the second testing session; a sensible strategy for a repeated-measures design. We did not consider enriched samples to introduce selection bias for this review question, because we were interested on the effect of the manipulation on secondary hypersensitivity, rather than the effect of the induction on secondary hypersensitivity. Rather, we considered an enriched sample to increase confidence that secondary hypersensitivity was indeed induced. Overall, our results may not fully capture all manipulation effects, given that the efficacy or reproducibility of the induction itself could not be verified in 24 of 27 studies.

Strengths and Limitations of This Review

This review used strategies to optimize rigor and clarity: we followed a published protocol, reported all deviations from protocol, and used best-practice duplicate reviewing. However, as in all reviews, the quality of the review findings depend on the quality of the primary data. Pain rating scales varied across the eligible studies: scale anchors differed, and 4 (of 27) studies used a scale with a "non-painful" range, making comparison across studies difficult. Standardized scales for sensation and pain rating would better support comparison of manipulations of secondary hypersensitivity. Much of the data for this review were extracted from plots, because few studies reported raw or usable summary data. Public sharing of raw data (eg, platforms such as open science framework,[82]) would facilitate future reviews. Additionally, there were a wide range of experimental models used to induce secondary hypersensitivity. This heterogeneity among the induction models reduces the comparability of the effects of manipulations on pinprick perception and surface area of secondary hypersensitivity.

Conclusion

This review found that several non-pharmacological manipulations are reported to influence the magnitude and surface area of secondary hypersensitivity: manipulations of attention, anodal transcranial direct current stimulation, hyperbaric oxygen therapy, written emotional disclosure, cognitive behavioral therapy, spinal manipulation, placebo analgesia, nicotine deprivation, negative suggestion, or sleep disruption (male participants only). The largest bodies of evidence were for thermal stimulation (n = 6), manipulations of attention (n = 5), transcranial direct current stimulation (n = 4), and hyperbaric oxygen therapy (n = 2), whereas the remaining 10 manipulations were supported by a maximum of one dataset each. As such, the evidence base for this question remains small. Opportunities to improve methodological rigor to foster greater clarity exist. A substantial body of rigorous evidence on this topic would be of value, given its potential to clarify the effects of various non-pharmacological manipulations on the clinical feature of secondary hypersensitivity, and to pave the way for systematic, mechanistically motivated development and testing of novel therapies for clinical conditions in which secondary hypersensitivity is prominent.

Appendix A. Supporting information

Supplementary data associated with this article can be found in the online version at doi:10.1016/j.jpain.2023.06.013.

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